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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1956

ORIGINAL ARTICLES

STUDIES ON N-ALLYLNORMORPHINE IN MAN: ANTAGONISM TO MORPHINE AND HEROIN AND EFFECTS OF MIXTURES OF N-ALLYLNORMORPHINE AND MORPHINE

By H. F. Fraser, M.D.

G. D. Van Horn

and

Harris Isbell, M.D.

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N-ALLYLNORMORPHINE, or nalorphine (NAM), has been shown to antagonize the respiratory depression due to poisoning by morphine, methadone, dihydromorphinone, methorphinan, meperidine and heroin in man (Eckenhoff and associates[5,6]; Fraser *et al.*[8]; Chase *et al.*[3]; Bornstein *et al.*[1]; and Strober[13]). Moreover, NAM antagonizes many other actions of morphine; for example, analgesia, hypnosis and antidiuresis in rats; miosis, emesis and hypothermia in dogs; and excitement and mydriasis in cats (Orahovats *et al.*[12]; Winter *et al.*[18]; and Unna[14]). Isbell and Fraser[10] reported that the symptoms of abstinence from morphine were intensified by NAM. Wikler *et al.*[15], observed that 5 to 10 mg. of NAM precipitated characteristic morphine-like abstinence syndromes in patients addicted to morphine, heroin or methadone. Mild NAM-induced abstinence syndromes occurred after only 2 to 3 days' administration of therapeutic doses of any of these drugs. They also stated that the "euphoric" effects which followed the administration of single doses of morphine, methadone and heroin to nontolerant former addicts were antagonized by NAM but no abstinence phenomena were observed.

Recent clinical studies have indicated that mixtures of morphine and NAM[2] and of levorphan and levallorphan[4] are effective analgesics. Since NAM antagonizes "euphoria" induced by morphine and precipitates symptoms of abstinence, it is possible that such mixtures would be "pain relieving," while concurrently possessing reduced addiction liability. These experiments were, therefore, undertaken to amplify our knowledge of morphine antagonism by NAM and to present observations on the pharmacological properties of mixtures of NAM with morphine and with heroin. In addition,

a study of NAM administered orally will be reported.

Methods. All subjects were former opiate addicts who volunteered for the experiment. Eight men were used in testing any given series of compounds, including a placebo. Each man served as his own control. Objective observations included the measurements of the effects of the various drugs on pupillary diameter, respiratory minute volume, rectal temperature, pulse and respiratory rates, and systolic and diastolic blood pressure. The subjects were also observed closely for evidence of behavior resembling that seen after administration of morphine and were questioned at intervals concerning symptoms of morphine-like "euphoria." The methods used have been described in detail[9]. All drugs were administered subcutaneously unless otherwise specified. Mixtures of drugs were prepared in a solution of isotonic sodium chloride and were administered in the same syringe. Morphine was administered as the sulfate and NAM and heroin as the hydrochloride.

Results. EFFECT OF SINGLE DOSES OF MORPHINE AND NAM. The effects of 30 mg. of morphine, 3, 6 and 10 mg. of NAM and a placebo (water) on pupillary diameter, respiratory minute volume and rectal temperature are shown in Fig. 1. Constriction of the pupil induced by morphine was pronounced. Although miosis after NAM was slight, three or more points on the time action curves after 3, 6 and 10 mg. of NAM showed a statistically significant difference as compared with a placebo. Respiratory minute volume was decreased by 3, 6 and 10 mg. of NAM and by 30 mg. of morphine. During the first 2 to 3 hours after medication there was no significant difference in the respiratory depression induced by morphine and that induced by any dose of NAM. Rectal temperature was depressed by morphine and by all doses of NAM; in fact, 10 mg. of NAM consistently reduced body temperature more than did 30 mg. of morphine. The relatively short pharmacological action of NAM (2½ to 3 hours) is illustrated in this figure. Pulse and respiratory rates and blood pressure showed no significant changes.

ANTAGONISM OF SINGLE DOSES OF MORPHINE BY NAM. In this experiment 10 mg. of NAM were administered 1¾ hours after 30 mg. of morphine. Figure 2 shows that the miosis provoked by morphine was promptly and significantly antagonized by 10 mg. of NAM. In the same experiment, the respiratory depression induced by morphine was not counteracted by NAM. This figure also emphasizes the fact that NAM *per se* significantly depresses respiratory minute volume. The "euphoria" induced by the morphine was greatly reduced for 2 to 3 hours after NAM but thereafter it returned. Observations other than those mentioned were negative.

MIXTURES OF MORPHINE AND NAM AS COMPARED WITH MORPHINE ALONE. In these experiments the effect of 30 mg. of morphine alone was compared with the effect of 30 mg. of morphine mixed in the same syringe with 3, 6 and 10 mg. of NAM. When the amount of NAM in the mixture was increased, the miotic effect of morphine was reduced progressively (Fig. 3). This antagonism persisted for only about 3 hours. Both morphine alone and mixtures with NAM depressed respiration in a comparable manner. There was no indication that NAM counteracted the drop in rectal temperature caused by morphine; in fact, the reverse was observed since the decline in rectal temperature occurred more consistently after mixtures of morphine and NAM than after morphine alone. NAM interfered with "euphoria" induced by morphine for about 2 to 3 hours; thereafter, behavioral effects resembling those seen after morphine alone became evident. No significant effects on other measurements were observed.

NAM ORALLY. Since morphine given

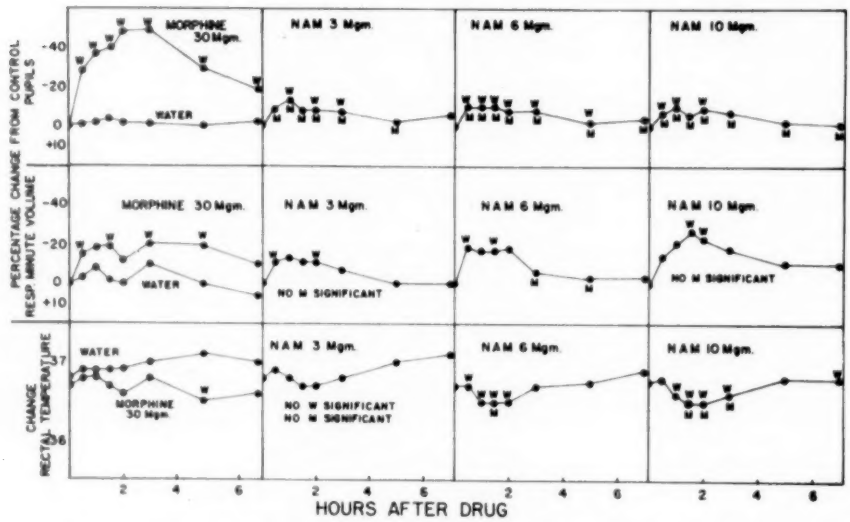

Fig. 1.—Effects of 30 mg. of morphine sulfate, 3, 6 and 10 mg. of NAM, and a placebo (water) administered subcutaneously at zero time on pupillary diameter, respiratory minute volume and rectal temperature. Each point on each curve represents the mean of results obtained on 8 subjects. The letter "W" denotes a statistically significant difference ($p<0.05$) of that value as compared with water. The letter "M" indicates a statistically significant difference between that point and an equivalent point for morphine sulfate. The absence of letters "W" and "M" indicates that such values are *not* significantly different, statistically.

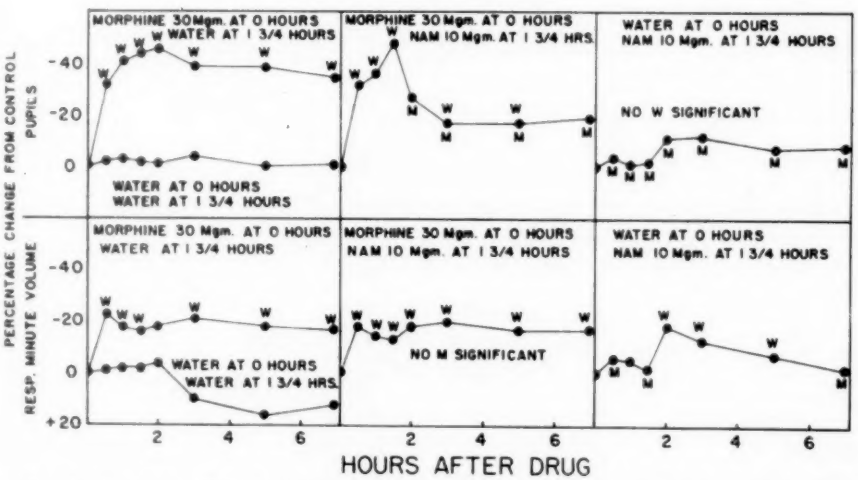
MORPHINE 30 Mgm. AT 0 HOURS
WATER AT 1 3/4 HOURS
MORPHINE 30 Mgm. AT 0 HOURS
NAM 10 Mgm. AT 1 3/4 HRS.
WATER AT 0 HOURS
NAM 10 Mgm. AT 1 3/4 HOURS
NO W SIGNIFICANT
WATER AT 0 HOURS
WATER AT 1 3/4 HOURS
MORPHINE 30 Mgm. AT 0 HOURS
WATER AT 1 3/4 HOURS
MORPHINE 30 Mgm. AT 0 HOURS
NAM 10 Mgm. AT 1 3/4 HOURS
WATER AT 0 HOURS
NAM 10 Mgm. AT 1 3/4 HOURS
NO M SIGNIFICANT
WATER AT 0 HOURS
WATER AT 1 3/4 HRS.
PERCENTAGE CHANGE FROM CONTROL
PUPILS
RESP. MINUTE VOLUME
HOURS AFTER DRUG

Fig. 2.—Antagonistic effect (measured by effect on pupillary diameter and respiratory minute volume) of 10 mg. of NAM administered subcutaneously 1¾ hours after 30 mg. of morphine. These results are compared with a placebo (water) for each condition. Each point on each curve represents an average of results obtained on 8 subjects. The letters "W" and "M" have the same significance as in Fig. 1.

orally has little "euphoric" and miotic effect[9], it was thought that NAM given orally would have much less activity than when administered subcutaneously or intravenously. To test this hypothesis, NAM was administered in doses ranging between 5 to 300 mg. orally to 8 postaddicts who had not received any narcotic for at least one week. Mild to moderate subjective symptoms were observed after 300 mg. NAM administered orally 2 hours prior to 30 mg. of morphine did not counteract either the miotic or respiratory depressant effects of morphine. In this experiment, particular attention was given to the degree of morphine-like "euphoria" and behavior which prevailed following intravenous injection of 30 mg. of morphine preceded by an oral placebo, as compared with that which occurred when 30 mg. of mor-

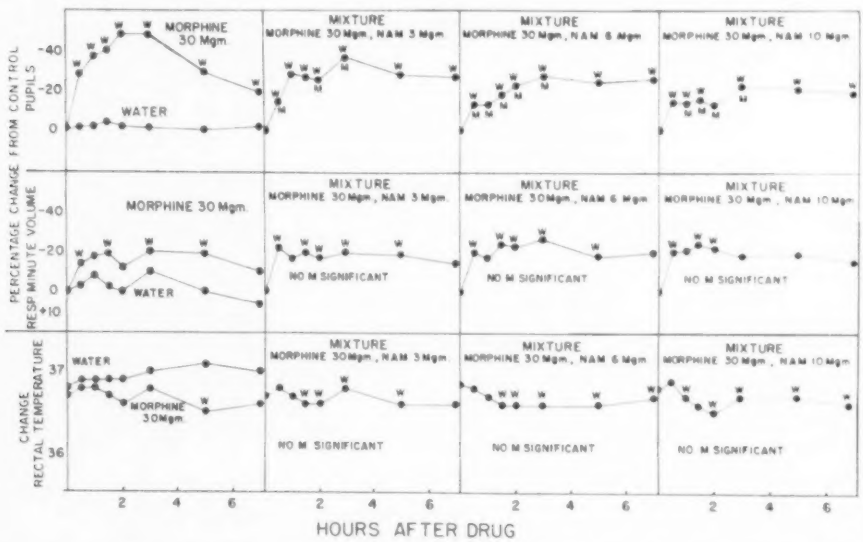

Fig. 3.—Effects on pupillary diameter, respiratory minute volume and rectal temperature of 30 mg. of morphine and mixtures of 30 mg. of morphine with 3, 6 and 10 mg. of NAM. All compounds, including the placebo (water) were administered subcutaneously at zero time. Each point on each curve represents the average of results obtained on 8 subjects. The letters "W" and "M" have the same significance as in Fig. 1.

of NAM in 4 of the 8 men. Two of these men were given an additional 300 mg. of NAM 3 hours after the first dose. No appreciable augmentation of the subjective effects occurred.

In another experiment, the effectiveness of orally administered NAM in counteracting the "euphoria" and other effects of morphine was evaluated. Ten postaddicts were used and drug combinations were given in randomized order. As shown in Fig. 4, 300 mg. of phine intravenously was preceded by 300 mg. of NAM orally. An observer, who was unaware of the medication schedule, watched each man carefully while he was being given the intravenous injection and for 6 hours subsequently, to ascertain if behavior resembling that which develops after morphine appeared. Patients were also questioned to determine whether a morphine-like "euphoria" resulted. These experiments showed that prior

oral administration of NAM appreciably blocked morphine-like "euphoria" and morphine-like behavior. Nearly all of these patients said at first "that is just like morphine," but within 2 or 3 minutes they began to protest that the morphine-like effect (vasomotor flush, urticaria, "turning of the stomach and drive") was receding too rapidly. However, there was evidence of return of the morphine-like "euphoria" and characteristic behavior after 5 or 6 hours. When morphine was given 24 hours after 300 mg. of NAM there was no indication of any interference with morphine-like "euphoria."

Single doses of 300 mg. of NAM orally had no significant effects on pulse rate, respiratory rate, blood pressure and rectal temperature.

In order to ascertain the oral dose required to precipitate abstinence from morphine, NAM was administered orally 30 minutes after the regular dose of morphine to 4 patients who had been stabilized on 120 to 300 mg. of morphine daily. Seventy-five milligrams of NAM orally provoked mild symptoms of abstinence, 120 mg. moderate abstinence, and 240 mg., severe abstinence. By comparison, when given subcutaneously, 2 mg. of NAM precipitated symptoms of mild abstinence, 3 to 4 mg., moderate abstinence, and 5 to 10 mg., severe abstinence.

MIXTURE OF DIACETYLMORPHINE (HEROIN) AND NAM. In 8 patients, a mixture of 10 mg. of heroin and 10 mg. of NAM given subcutaneously in the same syringe caused significantly less miosis than did 10 mg. of heroin alone (Fig. 5). Heroin caused no significant depression of minute volume (as compared with placebo). This strange result may have been due to the fact that the pre-drug values for respiratory minute volume were high in 7 of the 8 patients on the day the placebo was given. It is clear, however, that NAM had no significant antagonistic effect

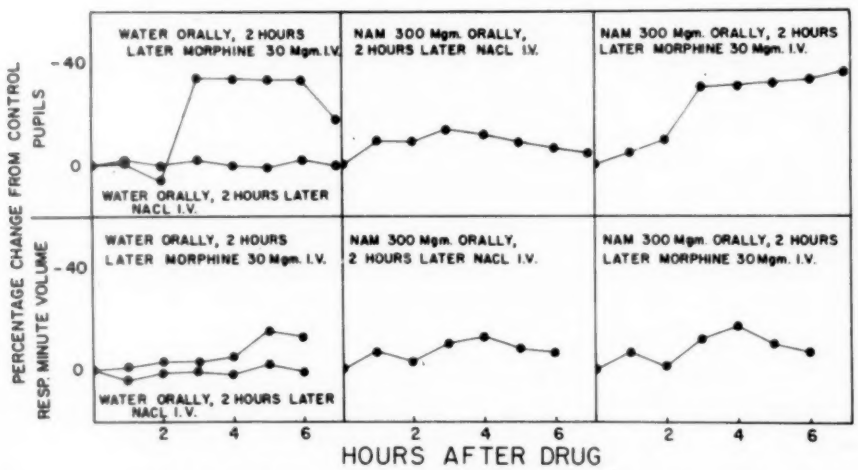
WATER ORALLY, 2 HOURS LATER MORPHINE 30 Mgm. I.V.
NAM 300 Mgm. ORALLY, 2 HOURS LATER NACL I.V.
NAM 300 Mgm. ORALLY, 2 HOURS LATER MORPHINE 30 Mgm. I.V.
PERCENTAGE CHANGE FROM CONTROL
PUPILS
-40
0
WATER ORALLY, 2 HOURS LATER NACL I.V.
RESP. MINUTE VOLUME
2
4
6
HOURS AFTER DRUG

Fig. 4.—Antagonistic effect of 300 mg. of NAM administered orally 2 hours prior to 30 mg. of morphine intravenously. These results are compared with those after placebos (bitter water substituted for oral NAM; NaCl solution i.v., substituted for morphine). Each point on each curve represents an average of results obtained on 5 to 8 subjects. The number of subjects that completed the experiment was insufficient for statistical treatment of the data.

on heroin-induced respiratory depression. As was the case with morphine, NAM did not reverse the lowering of body temperature caused by heroin.

Discussion. Wikler[16] has shown that a large dose (60 mg.) of NAM depresses rectal temperature and respiratory rate and that 60 mg. of NAM would not counteract the depression of rectal temperature which followed administration of 30 mg. of morphine. In this study, doses of NAM as small as 3 to 10 mg. significantly depressed respiratory minute volume and body temperature. This compound, therefore, possesses certain undesirable actions. It is interesting too, that 3, 6 or 10 mg. of NAM did not block or reverse the respiratory depression induced by 30 mg. of morphine in these former addicts. Lasagna and Beecher[11] have obtained similar results in non-addicts. In contrast, the miotic and "euphoric" effects of morphine were blocked or reversed by NAM. It is, however, well known that NAM causes a marked increase in respiratory rate and minute volume in human patients poisoned with morphine[5], methadone[8], or heroin[13]. This apparent inconsistency may be explained if one assumes that NAM as compared with morphine has a considerably greater affinity for certain cell-receptors. Hence, when NAM

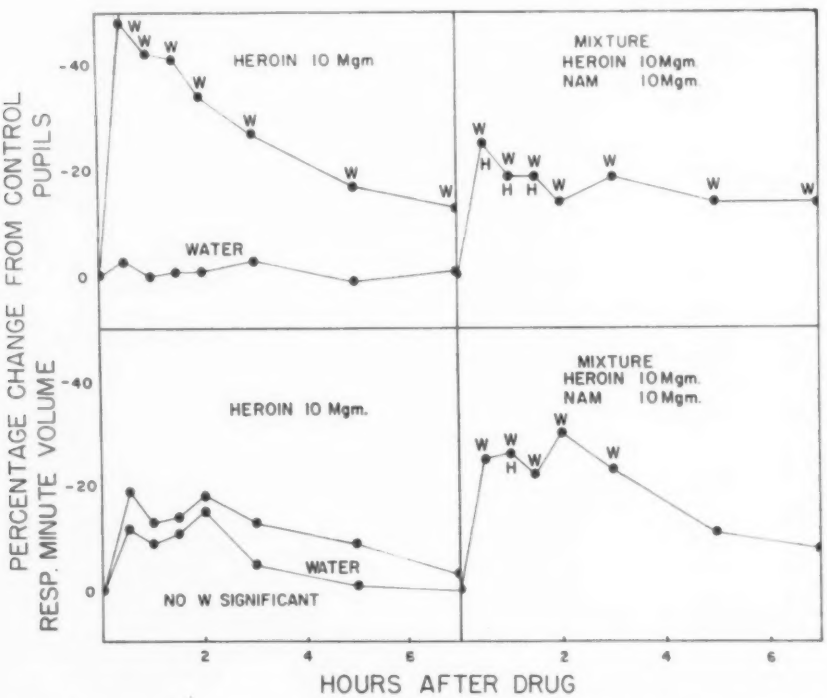

Fig. 5.—Effects of 10 mg. of diacetylmorphine (heroin) and of a mixture of 10 mg. of diacetylmorphine with 10 mg. of NAM on pupillary diameter and respiratory minute volume. All compounds, including the placebo (water), were administered subcutaneously at zero time. Each point on each curve represents the average of results obtained on 8 subjects. The letters "W" and "H" have the same significance as in Fig. 1.

is given concurrently with relatively small doses of morphine, the principal effect is that of NAM. Under these conditions, respiratory depression by morphine is replaced by an equivalent respiratory depression caused by NAM so that no antagonism of the morphine effect is apparent. When NAM is administered to patients seriously poisoned with morphine, NAM again competes more successfully than morphine for a site on the cell; the principal effect is again that of NAM. The marked respiratory depression due to morphine is replaced by a presumably milder respiratory depression due to NAM and so antagonistic effects appear to have occurred. Another explanation of these apparently contradictory phenomena is that the antagonistic action of NAM is contingent on the presence of some degree of physical dependence which, as suggested by Wikler and Carter[17], may develop after a single massive dose of morphine. Of course, both of these hypothesized mechanisms could operate concurrently.

The potential use of mixtures of NAM with morphine would be dependent upon NAM blocking the undesirable side effects of morphine (nausea, vomiting, respiratory depresson, and addiction) without impairing its analgesic activity. The work of Orahovats and associates[12] indicates that such differential blocking occurs in animals given mixtures of potent analgesics and limited amounts of NAM. Cappe and Pallin[2] reported that mixtures of NAM and morphine retained analgesic potency in obstetrical use and prevented respiratory depression in the newborn child. In a careful study, Lasagna and Beecher[11] found that 2 mg. of NAM did not interfere with the analgesic effects of 10 mg. of morphine. These investigators, on the other hand, found that respiratory depression after this mixture was as great as after morphine alone and, furthermore, the incidence of other untoward side effects of morphine (nausea, vomiting, and others) was not reduced by the addition of NAM. Lasagna and Beecher's results, together with those reported in this paper, suggest that mixtures of morphine and NAM are not likely to possess significant advantages over morphine alone under conditions of short-term use. However, because of conflicting reports, further clinical experimentation in this area seems desirable. Recently Cullen and Santos[4] have reported that another mixture (levorphan and levallorphan) induced analgesia without causing respiratory depression. On the other hand, Eckenhoff *et al.*[7] have found that a mixture of levallorphan with levo-Dromoran in a dosage relationship of 1:1 or 1:10 was not able to prevent the respiratory depression normally produced by levo-Dromoran. The same authors concluded that the mixture of opiates and opiate antagonists for the purpose of preserving analgesia and preventing respiratory depression is not worthwhile. It also remains to be determined whether such mixtures would decrease the rate at which tolerance and physical dependence develop under conditions of chronic use without impairing analgesic effect.

A suitable antagonist might have limited use in a manner similar to that of tetraethylthiuram disulfide (Antabuse) in the prevention of relapse following treatment of drug addiction. Properties desired in such a compound would include long length of antagonistic effects, minimal side effects, and reasonable efficacy when given orally. NAM, unfortunately, does not meet these requirements since it, like morphine, is relatively inert orally. The

short length of action and the disturbing side effects would also preclude NAM being used for this purpose.

Summary. 1. In former morphine addicts nalorphine (NAM) in doses of 3, 6 and 10 mg. subcutaneously, caused lowering of body temperature and depression of respiratory minute volume approximately equivalent to the effect of 30 mg. of morphine, and only slight pupillary constriction. No significant effects on pulse and respiratory rates or blood pressure occurred.

2. When NAM (3, 6 or 10 mg.) was given simultaneously with 30 mg. of morphine, or when 10 mg. of NAM was given 1¾ hours after 30 mg. of morphine, the "euphoric" and miotic effects of the morphine were blocked or diminished. Depression of body temperature and respiration induced by morphine, however, was not antagonized.

3. Ten milligrams of NAM administered simultaneously with 10 mg. of heroin antagonized the miotic but not the respiratory-depressant effect of the heroin.

4. NAM was effective orally but a much greater dose was required.

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(Interlingua on page 25)

TEN-YEAR PROGNOSIS OF ACUTE MYOCARDIAL INFARCTION

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Varied drugs and surgical procedures are currently being used in individuals who have had a myocardial infarction in an effort to influence the ultimate prognosis. Long-term follow-up studies of untreated patients are needed as controls in order to evaluate properly such agents. More must be written about the natural history of the disease.

In 1949 we[9] reported on the ultimate prognosis of 484 patients who had recovered from their first myocardial infarction and who lived more than 2 months. A 5-year survival study of a group of these patients showed that 61% lived more than 5 years.

The present report is a 10-year follow-up study of individuals who had recovered from their presumed first myocardial infarction and who lived more than 2 months. A survival period of 2 months was selected since by this time the majority of patients who will live have become ambulatory and are usually ready to resume a modified or regular routine of life. All the cases were seen in private practice. Only patients with characteristic clinical and electrocardiographic evidence were selected. Patients are often seen, particularly those with slowly progressive coronary artery disease, who must have had a myocardial infarction, but the date of the infarction cannot be determined. They were excluded from the study. A total of 227 individuals met the above criteria. The cases were seen from January 1, 1940, to July 1, 1945, and were followed until July 1, 1955. Of these, 16, or 7%, had inadequate follow-up. A total of 211 cases was then available for analysis. There were 170 males (80.5%) and 41 (19.5%) females.

Table 1 shows the course of the 211 cases as to a 10-year survival period. A total of 77 (36.5%) lived more than 10 years.

TABLE 1.—COURSE OF 211 CASES AS TO 10-YEAR SURVIVAL

Died Within 10 Years		*Survived 10 Years*	
No. of Cases	*% Total*	*No. of Cases*	*% Total*
134	63.5	77	36.5

TABLE 2.—DURATION OF LIFE
(134 Deaths Within 10 Years)

Period (Years)	*Total Deaths*	
	Number	*%*
0 to 1	17	12.7
1 to 2	17	12.7
2 to 3	18	13.4
3 to 4	15	11.2
4 to 5	17	12.8
5 to 6	12	9.0
6 to 7	14	10.5
7 to 8	8	5.9
8 to 9	8	5.9
9 to 10	8	5.9

Table 2 shows the duration of life by years of the 134 patients who died within 10 years. The mortality rate shows that most of the patients who will die do so in the first 5 years. Bland and White[1] found that the first year accounted for the greatest number of deaths; thereafter, the distribution of fatalities by years was not significant. Sigler[7] reported that the majority of

patients with a coronary occlusion who died did so within 4 years after the first attack.

Table 3 shows the sex factor as to survival for more than a decade. The number of each sex who died within 10 years was approximately the same.

Table 4 is an analysis of the factors in mortality and 10-year survival as to sex and age at the time of onset of the myocardial infarction. It is obvious that more young people will live more than 10 years after an infarction than those

TABLE 3.—DISTRIBUTION OF PATIENTS BY SEX

	Died Within 10 Years		*Survived 10 Years*	
Sex	*Number*	*% of Total*	*Number*	*% of Total*
Male	110	64.7	60	35.3
Female	24	59.0	17	41.0
Total	134		77	

TABLE 4.—AGE AT TIME OF ONSET, SEX DISTRIBUTION AND SURVIVAL

	Died Within 10 Years		*Survived Over 10 Years*			
Age (Years)	*Male*	*Female*	*Male*	*Female*	*Total Male*	*Total Female*
20 to 39	6	0	10	0	16	0
40 to 49	20	1	18	1	38	2
50 to 59	36	6	22	7	58	13
60 to 69	40	9	10	9	50	18
70 to 89	8	8	0	0	8	8

whose age at the time of the infarction was 70 years or beyond. Thus, of 16 men whose age at the time of onset was below 40 years, 10 (62.5%) survived more than 10 years, whereas no patient age 70 or older survived more than 10 years. Smith[8] found no definite relation between age of onset and survival time. Other investigators[1,3,4] report a definite relationship similar to our observations.

No attempt was made to make a statistical analysis as to 10-year survival based on the functional status of the heart immediately after the 2-month survival of the initial myocardial infarction. Obviously the patient who has made a good functional recovery will live longer than one who survives the initial impact disabled by congestive heart failure, angina pectoris or a cerebral embolism. We have previously[10] stated that the complaints of the patient are the best guide to longevity and that elaborate hemodynamic studies to determine the integrity of the myocardium or the coronary circulation are not necessary. Bland and White[1] found that 34% of their 162 patients who survived the acute attack recovered completely in that they were able to carry on without cardiac symptoms. The course of this group was the most favorable in that 56% survived the first decade. Master and Jaffe[5] found that 27.7% of 180 patients who had suffered a coronary occlusion and who had made a complete functional recovery lived more than 10 years after their first attack. Cole *et al.*[3], have reported that of those patients who were able to return to complete activity, 71% lived over 10 years, compared with 10% who lived over 2 months up to 5 years. On the

other hand, of those who were bedridden, 85% lived over 2 months up to 5 years, and only 8% lived more than 10 years. Chapman and Fraser[2] examined the cardiovascular response to an exercise test in asymptomatic patients with healed myocardial infarction. The response was substantially the same, quantitatively and qualitatively, as to the response in comparable normal individuals.

Economic rehabilitation following a 2-month survival period was previously analyzed[11]. Seventy-six per cent of the patients in that report made a complete or partial economic recovery. In general, economic rehabilitation paralleled the functional cardiac status, but some individuals successfully returned to their former occupations despite symptoms of anginal or congestive heart failure. The work status of all the patients naturally altered as they became older, had another myocardial infarction, manifested angina pectoris, congestive heart failure, and the like. In this report, 76% of the 60 men who survived a decade were still at work. Others were able to work but had elected to retire.

Up to July 1, 1955, 145 patients had died. As shown in Table 1, 134 patients died within 10 years. The cause for death was known in 142 cases. These causes are listed in Table 5. The major cause of death, 88%, was cardiovascular disease. This included sudden or relatively sudden death; a new myocardial infarction; congestive heart failure; and cerebrovascular accidents. Electrocardiographic proof of a new myocardial infarction was not always available. Pulmonary embolism is not listed as a mode of death because there were no proven cases. Few necropsies were performed. The high incidence of death from cardiovascular disease after survival from the first myocardial infarction is mentioned in the literature[3-5].

Discussion. There are only a few reported 10-year prognostic studies of patients who have had a myocardial infarction. Comparison is not always possible since the time after survival is variously calculated, such as from the time of onset, one month, or as in this study, 2 months after the initial attack. Bland and White[1] reported that

TABLE 5.—CAUSE OF DEATH
(142 Cases)

	Number	%
Myocardial Infarction	55	38.7
Congestive Heart Failure	33	23.3
Cerebrovascular Disease	10	7.0
Sudden	27	19.0
Other	17	12.0

of 162 consecutive patients with a myocardial infarction who lived more than a month, 50, or 31%, survived 10 years. Smith[8] followed 100 consecutive patients with coronary thrombosis from 1930 to 1941. Of 81 cases who survived more than 2 months, 30, or 37%, survived more than 10 years. Fifteen patients (18.5%) were lost to follow-up. Robb and Marks[6] followed 166 men who had an acute coronary occlusion and who reported or admitted to disability on their life insurance policies. One-half survived more than 10 years. There is no mention in their report of the date of onset of the coronary occlusion. Cole, Singian and Katz[3] studied 356 patients who survived at least 2 months after their first infarction. Follow-up was incomplete in 20%. Of the 285 cases finally analyzed, two-fifths (43.9%) lived over 10 years. The more complete the follow-up, the less will be the percentage of patients who live more than a decade. Our follow-up was complete in 93%.

Summary and Conclusions. A 10-year follow-up study was made of 211 indi-

viduals who lived more than 2 months after their first myocardial infarction.

One-third lived more than 10 years.

The majority of those who died did so in the first 5 years.

More young people live more than 10 years after an infarction than do those in the older age groups.

The patient who has made a good functional recovery lives longer than those who are disabled by congestive heart failure, angina pectoris or a cerebral embolism.

Three-fourths of the patients made a complete or partial economic recovery.

The major cause of death, 88%, was cardiovascular disease.

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SUMMARIO IN INTERLINGUA

Decenne Prognose de Acute Infarcimento Myocardial

Esseva facite un decenne studio sequential de 211 individuos qui superviveva al minus 2 menses a lor prime infarcimento myocardial.

Un tertio superviveva plus que 10 annos.

Le majoritate del mortes occurreva durante le prime 5 annos.

Superviveva plus que 10 annos al infarcimento un plus grande numero de personas juvene que de personas in le gruppos de plus avantiate etates.

Patientes con bon recuperation functional superviveva plus longe que patientes invalidate per disfallimento congestive del corde, angina de pectore, o embolismo cerebral.

Tres quartos del patientes attingeva partial o complete rehabilitation economic.

Le principal causa de morte, 88 pro cento, esseva morbo cardiovascular.

THE SKIN RESPONSE TO A NICOTINIC ACID ESTER: AN ACUTE PHASE REACTION

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Acute inflammatory diseases are associated with various changes in the blood which can be detected with appropriate methods of measurement. These include the erythrocyte sedimentation rate, C-reactive protein, mucopolysaccharides, hyaluronidase inhibitor, and others. Such changes are called acute phase reactions because they appear early in the course of the illness and then disappear with clinical recovery. Special interest attaches to these changes in acute rheumatic fever and rheumatoid arthritis because, in the absence of specific diagnostic tests for these diseases, the acute phase reactions are useful in following the activity of the pathological process.

Recently a new type of acute phase reaction has been described, involving not the blood but the reactivity of the minute skin vessels in response to the vasodilating effect of nicotinic acid. It has been reported that the tetrahydrofurfuryl ester of nicotinic acid, when applied to the skin as a 5% ointment**, produces erythema within 30 minutes in normal individuals but results in actual blanching or no reaction at all in most children with active rheumatic fever[9,11] and a majority of adults with active rheumatoid arthritis[6,7,13]. Apparently no systematic study of this acute phase reaction has been made in other acute inflammatory diseases. It is the purpose of this paper to report such an investigation and it will be shown that the nicotinic acid ester skin reaction is nonspecific.

Method and Material. The skin test is performed as follows: The ointment is supplied in collapsible tubes and is squeezed into the open barrel of a tuberculin syringe. The piston is then inserted into the barrel of the syringe, avoiding the formation of air bubbles. Seventy milligrams of ointment has an approximate volume of 0.07 ml. and this amount is squeezed from the syringe on to the skin of the volar surface of the forearm. The ointment is then smeared over a circular area approximately 2.5 cm. in diameter with five or six circular strokes. The observer uses a rubber-encased finger for this purpose in order to avoid producing erythema of his own skin. The patient is cautioned to avoid smearing the ointment because, if his response is one of erythema, then the skin will redden wherever the ointment comes into contact with it. After 30 minutes the ointment is removed by washing the skin gently with an alcohol sponge, and the reaction is then read. It is difficult to read the reaction in heavily pigmented skin and therefore few Negroes were included in this series.

For the first 100 tests a control ointment containing all ingredients except the ester of nicotinic acid was applied to the skin of the other arm. No reactions were observed with the control ointment and so its use was discontinued thereafter. Saslaw and Streitfeld[9,11] described using 35 circular strokes to smear the ointment and this method was used for the first 100 tests. At this point 25 patients were tested on both forearms, using 35 strokes on one arm and merely 5 or 6 on the other. The results were identical and thereafter the lesser number of strokes was used for the sake of convenience.

Several types of reaction were evident as described by Saslaw and Streitfeld[9,11]. The normal or typical reaction consisted of varying

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**"Trafuril" ointment, generously supplied for investigation by Ciba Pharmaceutical Products, Inc., Summit, N. J.

degrees of erythema sometimes with slight edema at the site of application of the ointment, with or without an erythematous flare beyond the site. The abnormal or atypical reaction consisted of an actual blanching or no response at all in the area of application, with or without a surrounding flare. The degree of flare was not taken into consideration in interpretation of the test. Occasionally it may be difficult to tell whether there is any erythematous response and such a reaction is simply listed as questionable. The test is read in daylight preferably. Also occasionally the redness of the flare may be much greater than the degree of erythema noted at the site of application of the ointment. Since this was never seen in normal individuals and was seldom seen in patients, it was classified as abnormal in this series of cases. It probably represents a transition between the atypical and typical reactions.

After the ointment was removed, the erythema usually disappeared in several hours but sometimes it persisted for as long as 12 hours or more. This was probably due to inadequate removal of the ointment. An erythematous response was frequently associated with mild tingling, itching or burning sensation but this was not troublesome and could be relieved by antihistaminic drugs.

A total of 305 individuals was tested by this method, many repeatedly. The results were recorded descriptively and classified as typical, atypical or questionable. The persons tested included 56 presumably normal young adult basic trainees at this Base. Most of the remainder consisted of routine consecutive admissions to a general medical ward, all were males and most were in the 17 to 25-year-age group. There was some selection of cases in that, in addition to general medical admissions, this ward served as the center for all cases of nontuberculous pulmonary disease among enlisted men as well as acute respiratory infections. In addition, a series of patients with bacteriologically confirmed tuberculosis were tested.

In a series of 28 patients with acute follicular tonsillitis having an atypical skin test on admission to the hospital, the effect of large doses of oral nicotinamide was determined. After the initial test, nicotinamide was administered in a dose of 800 mg. per day in divided doses to alternate cases and the test was repeated daily for 5 days. All patients were treated with broad spectrum antibiotics.

The effect of oral isoniazid was determined in 42 patients who had normal reactions. Following the initial test, a single dose of 100 to 300 mg. of isoniazid was given by mouth and the test was then repeated from one to two hours later.

Results. For the purpose of this report, the results in a selected series of 237 individuals were analyzed. Results in the remaining 68 patients fell into numerous diagnostic categories and the number in each group was too small to permit reliable inferences to be drawn.

TABLE 1.—THE NICOTINIC ACID ESTER SKIN TEST IN INFLAMMATORY DISEASE

Diagnosis	*No. of Cases*	*% Atypical*
Normal	56	0
Tonsillitis	64	89
U.R.I.	27	70
Pneumonia	22	68
Active tuberculosis	33	3
Noninflammatory disease	35	6

In Table 1 are presented the diagnostic categories with the number of cases in each and the percentage of these which had atypical skin tests. None of the 56 normal persons showed atypical tests. Of 64 patients with acute follicular tonsillitis 51 or 80% had atypical tests on admission to the hospital. Of the 13 cases whose skin test was typical on admission, 9 were retested several times during the course of the disease and 6 of these became atypical, bringing the total of atypical tests to 89%. If the other 4 typical cases had been retested also, the percentage of atypical patients might have been a little higher. It was noted that the patients who had typical reactions on admission and later converted to atypical had been sick for less than 48 hours when admitted to the hospital. Those who did not convert to atypical were mild cases with little or no constitutional reaction to the inflammation as judged by the absence of fever and leukocytosis.

The percentage of atypical tests was also high in other types of acute

respiratory infection: 70% of 27 patients with undifferentiated respiratory infection and 68% of 22 patients with pneumonia. In contrast, only 3% of 33 patients with active tuberculosis and 6% of 35 patients with various noninflammatory diseases showed atypical reactions. The latter group included 8 diabetics (of whom one had an atypical test), 7 patients with duodenal ulcer (of whom one had an atypical test), and smaller numbers of patients with hypertension, neurosis, malignancy, protruded intervertebral disc, coronary atherosclerosis, and others.

Among the 68 cases not listed in Table 1, there were 13 patients with bronchiectasis, 3 of whom had an atypical test; 8 asthmatics, 2 of whom had an atypical reaction; 7 patients with coccidioidomas, one of whom had an atypical reaction; and smaller numbers of patients with various other diagnoses. Two patients with active rheumatic fever had atypical tests, whereas 2 with inactive rheumatic fever had normal reactions.

A review of the cases with inflammatory diseases in those categories associated with typical reactions in some of the patients suggested that there was some correlation between the result of the test and the degree of constitutional reaction to the disease. This correlation is demonstrated in Table 2 for the 22 cases of bronchopneumonia. The etiology in these patients was not established by special studies. Sputum cultures generally revealed no specific pathogens, a beta hemolytic streptococcus, or pneumococcus. Treatment consisted of oral penicillin. Of the 7 patients who had a typical skin reaction on admission to the hospital, none had a white cell count of more than 10,000 per c.mm. or an increase of the percentage of polymorphonuclears to 80% or more and only 2 showed a maximum temperature of more than 100° F. In contrast, of the 15 patients with an atypical test, a majority showed leukocytosis and a maximum temperature rise to more than 100° F. No such correlation was found with elevation of the erythrocyte sedimentation rate.

To demonstrate that the nicotinic acid ester skin test is an acute phase reaction, some patients with tonsillitis and pneumonia were retested at weekly intervals. The results are shown in Table 3. Of 16 patients with tonsillitis, 14 had a normal test when retested one week later and only 2 patients required two weeks to become normal. Of 13 patients with pneumonia who had an atypical test on admission to the hospital, 6 converted to normal reactions in one week, 4 in two weeks, 2 in three weeks, and 1 in four weeks. Among the patients with pneumonia, the duration of an abnormal skin test could not be correlated with the duration of the pneumonic process as observed on weekly chest roentgenograms but the number of cases in each subgroup is too small for such a study.

TABLE 2.—THE CORRELATION BETWEEN SYSTEMIC REACTIONS AND THE NICOTINIC ACID ESTER SKIN TEST IN PNEUMONIA

	With Typical Reaction	*With Atypical Reaction*
No. of cases	7	15
WBC over 10,000	0	10
Polys. 80% or more	0	7
Temp. over 100° F.	2	12
ESR over 15	5/6	8/10

The effect of oral nicotinamide in converting atypical skin reactions to normal in patients with tonsillitis is shown in Table 4. Of 14 patients not treated with nicotinamide, only 6 had converted to a normal reaction by the fifth day, whereas 13 of the 14 nicotinamide-treated cases had converted to normal in the same period of time. In the nicotinamide-treated cases, daily

testing revealed some irregularity of the conversion to normal and the normal reaction thus produced was usually mild in the degree of erythema.

The effect of a single oral dose of isoniazid is shown in Table 5. Only 2 patients given 100 mg. of isoniazid showed obliteration of the typical response to the ointment. This lack of effect of isoniazid on the erythema produced by the nicotinic acid ester is not associated with an abnormal nicotinic acid ester skin reaction and isoniazid seldom has any effect on the test.

Discussion. The nicotinic acid ester skin test is apparently an acute phase reaction which is related to the degree of constitutional response in acute inflammatory diseases of various kinds. It does not seem to be as sensitive as the sedimentation rate in our series of pneumonias but is considerably more sensitive than the temperature elevation, since the latter subsides to normal in a few days, whereas the former requires several weeks to convert to normal. The value of this test as an acute phase reaction requires further study and comparison with other acute phase reactions in common use. However, if the nicotinic acid ester skin test proves to be a reliable indicator of the degree of active inflammation in such diseases as acute rheumatic fever and rheumatoid arthritis, then it will certainly be a much more convenient test for the

TABLE 3.—NICOTINIC ACID ESTER SKIN TEST AS AN ACUTE PHASE REACTION

Diagnosis	*No. of Weeks for Test to Become Normal*	*No. of Cases*
Tonsillitis	1	14
	2	2
Pneumonia	1	6
	2	4
	3	2
	4	1

TABLE 4.—THE EFFECT OF NICOTINAMIDE ON THE NICOTINIC ACID ESTER SKIN TEST IN TONSILLITIS

	Controls	*Nicotinamide-treated Cases*
No. of cases	14	14
Skin test normal by 5th day	6	13

also demonstrated in tuberculous patients who were receiving long-term isoniazid therapy (Table 6). The results in patients with active tuberculosis are analyzed in Table 6 with respect to the type of therapy at the time of the test. Only one patient had an atypical skin reaction and he was receiving streptomycin and oxytetracycline, but other patients receiving these drugs showed a typical response. The patient with an atypical test also had a chronic prostatitis and *Strongyloides stercoralis* infestation of the bowel. It is thus apparent that a chronic infection such as tuberculosis

TABLE 5.—EFFECT OF A SINGLE ORAL DOSE OF ISONIAZID ON THE NICOTINIC ACID ESTER SKIN TEST IN NORMAL INDIVIDUALS

Oral Dose of INH	*No. Tested*	*No. with Reaction Obliterated*
100 mg.	14	2
200 mg.	14	0
300 mg.	14	0
Total	42	2

TABLE 6.—THE NICOTINIC ACID ESTER SKIN TEST IN ACTIVE TUBERCULOSIS

Drug Therapy	*No. of Cases*	*No. with Atypical Reactions*
None	7	0
SM–PAS	12	0
SM–INH or INH–PAS	12	0
SM–TM	2	1
Total	33	1

practitioner than other acute phase reactions which require laboratory facilities.

This skin reaction is nonspecific from a diagnostic standpoint. It bears no relation to infection with the beta hemolytic streptococcus, for in the present series of cases of acute follicular tonsillitis only 41% of the patients showed a beta hemolytic streptococcus in their throat cultures prior to antibiotic therapy. However, the atypical reaction seems to be specific for nicotinic acid since Oka[7] reported that other vasodilating agents produced the normal degree of erythema in patients with atypical responses to the nicotinic acid ester ointment. These other agents included intracutaneous acetylcholine, subcutaneous histamine, mechanical irritation, aetheroleum sinapis, and phenol in olive oil.

The mechanism of this skin test is unknown but the possibilities are intriguing. There is apparently no relationship to histamine, since Strehler[10] has reported that antihistamines have no effect upon the skin test although it was found by the present writer that the burning sensation occurring in some patients with a normal response can be relieved by a dose of an antihistamine. The hyperemia produced by the nicotinic acid ester is probably not due to liberation of acetylcholine since Oka[7] states that neostigmine does not convert atypical reactions to normal. ACTH and cortisone do convert atypical tests to normal but apparently this is not directly related to the skin reaction itself. Nassim and Banner[6] indicate that in patients with active rheumatoid arthritis atypical skin tests become typical only when the disease is controlled by the steroids.

Saslaw and Streitfeld[9] have suggested three possible mechanisms for the atypical skin reaction: 1) alteration of reactivity of the minute vessels, 2) disturbance of nicotinic acid metabolism, and 3) changes in hyaluronic acid metabolism. Little can be said about the first possibility since it is a vague concept at best. The fact that mechanical irritation of the skin and various other vasodilating agents produce hyperemia in patients with atypical skin tests would seem to be a point against such a mechanism.

Disturbance of nicotinic acid metabolism as a possible mechanism is an interesting one for speculation. The effect of nicotinamide in converting atypical tests to normal in patients with tonsillitis reported herein might suggest that patients with atypical tests have some degree of nicotinic acid deficiency, although this is not necessarily true. If the tissue of a patient were relatively unsaturated with nicotinic acid, then it is conceivable that the addition of a small amount of nicotinic acid to the skin in the form of an ointment might be inadequate to stimulate hyperemia. However such an hypothesis would require more evidence than is now available to support its validity. In the literature there is a small amount of information which is related to this matter.

The study of nicotinic acid blood levels in various disease states has been rather fruitless, since there is a tremendous overlap in these levels between pathological states and normals, even in the obvious nicotinic acid deficiency disease of pellagra. The same applies to studies of pyridine nucleotide measurements in the blood and almost all of the blood nicotinic acid is bound up in the cellular pyridine nucleotides (Coenzymes I and II). However, Vilter *et al.*[14] did report that blood coenzyme values were abnormally low in patients with pneumococcal pneumonia and these values became normal after crisis in most patients.

Studies of the urinary excretion of

nicotinic acid and its derivatives have been more rewarding and Braun and Grossowicz[3] have reported that patients with typhoid fever excrete less and less nicotinic acid and nicotinamide as the disease progresses into convalescence. Similar studies are needed in other acute infections.

In tuberculosis there does not seem to be any disturbance of nicotinic acid metabolism. Biehl and Vilter[2] have reported normal excretion of N'methyl nicotinamide (the major excretion product of nicotinic acid) in this disease. This correlates with the finding of normal nicotinic acid ester skin tests in tuberculous patients in the present investigation. Thus in yet another way does tuberculosis fail to produce the same systemic reverberations found in acute inflammatory diseases. The single tuberculous patient herein mentioned who had an atypical test was also infested with *Strongyloides stercoralis* and in relation to this it is of interest that Abbasy mentions that most cases of nicotinic acid deficiency in Egypt are associated with infestation by intestinal parasites[1].

Wooley[15] has been able to produce nicotinic acid deficiency in animals by administering 3-acetyl pyridine, an analogue of nicotinic acid. Several cases of pellagra[5,12] occurring in the course of isoniazid therapy for tuberculosis have been reported, and it has been suggested that isoniazid may substitute for nicotinamide in the pyridine nucleotide structure[8]. Isoniazid has a chemical structure very similar to that of nicotinic acid, although the side chain is in a different position on the pyridine ring. Therefore it was thought that the administration of isoniazid might have some effect on the nicotinic acid ester skin reaction. The results reported here do not support this idea and Biehl and Vilter[2] have shown that isoniazid does not cause any change in the excretion of N'methyl nicotinamide in tuberculous patients. Obvious pellagra in tuberculous patients treated with isoniazid is quite rare and it is likely that factors other than the drug therapy are more important in such cases. Further studies of nicotinic acid metabolism in relation to the nicotinic acid ester skin test are indicated and are under way.

Grais and Glick[4] have reported that acute rheumatic fever and various acute infections as well as disseminated malignancy are associated with an increase in nonspecific hyaluronidase inhibitor in the blood. It is therefore conceivable that this acute phase reaction and the nicotinic acid ester skin response have a cause and effect relationship. One might expect that increase in hyaluronidase inhibitor would tend to prevent the penetration and spread of the nicotinic acid ester through the skin. Although the same rationale may be applied to the effect of other vasodilating agents put on the skin, the quantitative relationships may differ. Investigation along this line may be worthwhile.

Summary. Application of an ointment containing 5% tetrahydrofurfuryl ester of nicotinic acid to the skin produces erythema within 30 minutes in normal individuals. No erythema or actual blanching occurs in most patients with acute inflammatory diseases, whereas normal reactions result in patients with tuberculosis or noninflammatory diseases. This test is a nonspecific acute phase reaction which is related to the degree of constitutional response to the inflammatory condition.

Administration of large oral doses of nicotinamide tends to convert the atypical reaction to normal sooner in patients with tonsillitis than in similar patients not receiving such treatment. This suggests that the atypical nico-

tinic acid ester skin test may be related to a disturbance of nicotinic acid metabolism, but further study of this matter is in progress. Other possible mechanisms have been discussed.

The nicotinic acid ester skin test warrants further investigation as an acute phase reaction because it has the advantages of simplicity and convenience.

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SUMMARIO IN INTERLINGUA

Le Responsa Cutanee a un Ester de Acido Nicotinic: Un Reaction del Phase Acute

Le application cutanee de un unguento a 5 pro cento de ester tetrahydrofurfurylic de acido nicotinic produce erythema intra 30 minutas in individuos normal. Nulle erythema o ver blanchimento occurre in le majoritate del patientes con acute morbos inflammatori, sed reactiones normal resulta in patientes con tuberculosis o morbos non-inflammatori. Iste test es un non-specific reaction del phase acute. Illo depende del grado de responsa constitutional al condition inflammatori.

Le administration oral de large doses de nicotinamido tende a normalisar le reaction atypic de patientes con tonsillitis plus promptemente que iste nomalisation occurre in simile patientes qui non recipe le mesme tractamento. Isto suggere que le atypic test cutanee a esteres de acido nicotinic es connectite con un disturbation del metabolismo de acido nicotinic, sed studios additional de iste question es in progresso. Altere possibile mechanismos es discutite.

Le teste cutanee a esteres de acido nicotinic merita investigationes additional como reaction del phase acute proque illo ha le avantages de simplicitate e commoditate.

NICOTINIC ACID BLOOD LEVELS IN RELATION TO THE SKIN RESPONSE TO A NICOTINIC ACID ESTER OINTMENT*

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In a previous report[6] it was shown that the application of an ointment containing 5% tetrahydrofurfuryl ester of nicotinic acid to the skin produces erythema within 30 minutes in normal individuals and patients with tuberculosis or noninflammatory diseases. In most patients with acute inflammatory diseases the reaction is atypical in that no erythema or actual blanching results. This atypical skin response is a nonspecific acute phase reaction which is related to the degree of constitutional disturbance produced by the inflammatory condition and reverts to normal as the acute disease subsides.

It was also shown that the administration of large oral doses of nicotinamide tends to convert the atypical reaction to normal sooner in patients with acute tonsillitis than in similar patients not receiving such treatment. This suggests that the atypical nicotinic acid ester skin response may be related to a disturbance of nicotinic acid metabolism. Therefore, a study of nicotinic acid blood levels in relationship to the skin response was undertaken and the results will be presented in this report.

Method and Material. Nicotinic acid blood levels were determined by the standard microbiological assay method as described in the U. S. Pharmacopoeia with the exception that blood was prepared for assay by the method of Isbell *et al.*[3]. A hematocrit was determined for each blood specimen and the results of the assay were calculated as nicotinic acid equivalents in gamma per ml. of whole blood and per ml. of packed red blood cells.

The skin test with the nicotinic acid ester ointment was done by the method previously described[6]. The results were recorded descriptively and classified as typical or atypical.

Blood level determinations were made in a series of presumably normal persons such as laboratory technicians and individuals reporting to the laboratory for routine examinations. Blood specimens were obtained approximately 2 hours after breakfast. In 4 laboratory technicians blood determinations were made in the fasting state and 1 or 2 hours after lunch. The persons in these groups were not skin tested.

Skin tests and blood levels were made in a series of patients with various diseases and the results were broken down according to whether the skin test was typical or atypical. In 15 patients with various acute infections and atypical skin tests on admission to the hospital, the skin tests and blood levels were repeated at weekly intervals to determine whether there were any significant trends as the patients recovered.

Results. Table 1 presents the nicotinic acid blood levels in several young male laboratory technicians in the fasting state and 1 hour after lunch. In each case the latter value was slightly greater than the former. When these determinations were repeated 1 week later in the same 3 individuals and 1 additional person with the afternoon specimen drawn 2 hours after lunch, the difference between the fasting and postprandial levels in each subject was greater. It should be noted that the fasting blood levels in the 3 individuals were examined twice, a week apart, and the second value varied as much as 23% below the first value.

*"Trafuril" ointment was generously supplied by, and the investigation was aided by a grant from Ciba Pharmaceutical Products, Inc.

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Table 2 gives the mean and range of nicotinic acid blood levels in 3 groups of persons, including 25 presumed normal individuals, 23 patients with a typical response to the nicotinic acid ester skin test and 30 patients with an atypical response to the ointment. The levels varied from 16.2 to 25.8 gamma per ml. of whole blood and from 32 to 58 gamma per ml. of packed red cells. It is obvious that the range was great and that there was no significant difference between the 3 groups.

Table 3 shows the nicotinic acid blood levels and simultaneous skin test results at weekly intervals in 15 patients who were admitted to the hospital with various acute inflammatory diseases and an atypical skin response to the nicotinic acid ester ointment. In 4 patients there was essentially no change in the values whether calculated for whole blood or packed red cells. In 2 cases there was little change in the whole blood concentration but there was more than 10% diminution in the red cell level. In 2 additional cases there was little change in the red cell level but there was more than 10% change in the whole blood level; in patient Ma, this consisted of a rise between the first and second determinations, whereas in patient Bu the nicotinic acid level first fell and then rose. In the remaining 7 patients there was a greater than 10% change in the nicotinic acid level for whole blood and for packed red cells, both in the same direction. In 1 of these 7 cases the change was downward; in 5 it was upward; and in one the levels first fell and then rose. Thus, although the number of patients is small, and all nicotinic acid blood levels were within the normal range, it appears that among those that showed more than 10% change in nicotinic acid blood or red cell levels, or both, (11 cases) all

TABLE 1.—FASTING AND POSTPRANDIAL NICOTINIC ACID BLOOD LEVELS

		Nicotinic Acid Equivalents in Gamma Per			
		ml. of Blood		*ml. of RBC*	
Name	*Date*	*Fasting*	*1 Hr. after Lunch*	*Fasting*	*1 Hr. after Lunch*
JA	Feb. 11	22.6	23.8	47	50
L	Feb. 11	21.4	22.4	43	45
R	Feb. 11	22.6	23.2	48	49
		Fasting	*2 Hrs. after Lunch*	*Fasting*	*2 Hrs. after Lunch*
JA	Feb. 19	19.4	22.6	40	47
L	Feb. 19	16.9	18.3	38	41
R	Feb. 19	17.5	20.4	35	41
JB	Feb. 19	18.4	21.7	38	45

TABLE 2.—NICOTINIC ACID BLOOD LEVELS IN PATIENTS WITH TYPICAL AND ATYPICAL NICOTINIC ACID ESTER SKIN TESTS

		Nicotinic Acid Equivalents in Gamma Per			
		ml. of Blood		*ml. of RBC*	
	Number	*Mean*	*Range*	*Mean*	*Range*
Skin test typical	23	21.3	16.3–25.8	46	38–51
Skin test atypical	30	19.9	16.2–24.0	44	32–55
Presumed normals	25	20.1	16.2–24.2	44	32–58

showed an increase except for 3 patients who had only two serial determinations made. The latter might have shown an increase after the initial fall if additional determinations had been made. However, no correlation can be made between the blood levels of nicotinic acid and the kind of response to the nicotinic acid ester skin test.

TABLE 3.—SERIAL NICOTINIC ACID ESTER SKIN TESTS AND NICOTINIC ACID BLOOD LEVELS IN PATIENTS WITH ACUTE INFECTIONS

Name	*Diagnosis*	*Skin Test*	*Nicotinic Acid Equivalents in Gamma Per*	
			ml. of Blood	*ml. of RBC*
Le	U.R.I.	Atypical	19.9	46
		Atypical	20.0	48
		Atypical	21.4	49
		Typical	20.5	50
Fi	Tonsillitis	Atypical	21.5	45
		Typical	20.2	42
Pf	Pneumonia	Atypical	19.4	45
		Atypical	19.0	48
		Atypical	20.8	45
Ba	Pharyngitis	Atypical	19.0	47
		Typical	20.2	50
He	U.R.I.	Atypical	22.4	52
		Typical	21.0	44
Ge	Pneumonia	Atypical	21.3	50
		Typical	20.8	43
Bu	Pneumonia	Atypical	19.1	42
		Atypical	17.6	41
		Typical	20.9	42
Ma	Pneumonia	Atypical	19.0	42
		Typical	16.3	40
An	U.R.I	Atypical	20.6	41
		Typical	22.5	51
Va	Pharyngitis	Atypical	21.2	46
		Atypical	19.7	40
		Atypical	17.1	36
		Atypical	24.0	52
Th	U.R.I.	Atypical	18.0	34
		Typical	21.4	46
Vi	Pneumonia	Atypical	16.2	32
		Atypical	17.5	38
		Atypical	20.8	43
Du	U.R.I.	Atypical	18.9	39
		Typical	20.8	51
		Typical	22.3	47
Mo	Pharyngitis	Atypical	20.1	39
		Typical	25.8	51
Ph	U.R.I.	Atypical	18.5	47
		Typical	16.4	41

Discussion. The determination of the concentration of nicotinic acid in the blood by the microbiological assay method is relatively simple but may not be very accurate because the final figure is obtained by averaging at least 3 measurements which fall within 10% of the mean. Furthermore, the method may not be specific for nicotinic acid and its amide. For example, isonicotinic acid hydrazide (INH) can support the growth of the test organism, *Lactobacillus arabinosus*, to a certain extent in the absence of nicotinic acid in the medium. This is illustrated in Fig. 1. Mixtures of nicotinic acid and isonicotinic acid hydrazide in the same medium have an additive growth promoting effect for the bacillus. Therefore, al-

though the term "nicotinic acid level" is used rather loosely in this report, it is more correct to speak of the measurement in terms of "nicotinic acid equivalents." Actually the method measures nicotinamide as well as the free acid.

In this investigation nicotinic acid blood levels have been calculated per unit of whole blood and per unit of packed red cells. The reason for this is that more than 95% of the vitamin in the blood resides within the red cells. However, it is possible that changes in serum level may be more significant than changes in whole blood levels and further investigation along this line is needed.

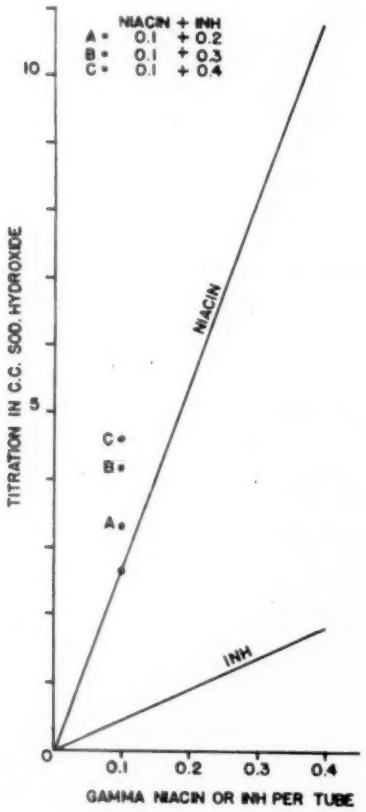

Fig. 1.—Growth curves for *Lactobacillus arabinosus* in tubes of medium containing increasing concentrations of nicotinic acid (niacin) or isoniazid (INH). The degree of growth is measured by the amount of acid produced in 72 hours of incubation as titrated with sodium hydroxide. Points A, B and C represent the amount of growth in tubes containing 0.1 gamma nicotinic acid plus 0.2 to 0.4 gamma isoniazid in order to show that the growth effect of these 2 substances is additive.

The blood levels found in this study are several times as high as other reports in the literature have indicated[23]. The explanation for this is not apparent. Almost all of the individuals tested were young adult males of military population and this may be significant.

The blood level results covered a rather wide range as has been found by other investigators. Even in the deficiency disease of pellagra, the blood concentrations of nicotinic acid have been reported in the low normal range[2]. Within this wide range of values, there was no apparent relation of the blood level to the kind of skin response to the nicotinic acid ester ointment. Therefore, if the atypical skin response to the ester of nicotinic acid reflects a disturbance of nicotinic acid metabolism in acute inflammatory diseases, other approaches to the problem will be necessary to reveal the relationship; for example, studies of urinary excretion or of tissue saturation of the vitamin.

It is difficult to interpret the changes in nicotinic acid blood levels which occurred in some of the patients with acute infections from week to week because, as was seen in the study of fasting blood levels in 3 laboratory technicians, the result may vary as much as 23% from one week to the next. Nevertheless, most of the changes which did occur among patients with acute infections consisted of an increase, or an increase after an initial decrease if the patient was followed long enough, as the disease subsided.

These findings may be a hint that there is indeed a disturbance of nicotinic acid metabolism in patients with acute infections, a disturbance which is not readily reflected in the blood concentration of the vitamin.

There have been very few studies of nicotinic acid metabolism in acute infectious diseases. Braun and Grossowicz[1] reported a study of the excretion of nicotinic acid (including its amide) by the microbiological assay method in 25 cases of typhoid fever. Blood levels were normal in 4 cases but almost all of the patients showed a gradual progressive decrease in urinary excretion of the vitamin, thought to be due to tissue depletion despite the fact that in most cases there were no clinical signs of vitamin deficiency. This occurred in only 1 of 9 patients with pneumonia and in 1 of 3 patients with typhus.

Almost all of the blood nicotinic acid is inside the red cell as an important part of the pyridine nucleotide structure (Coenzymes I and II). There have been two investigations of the concentrations of pyridine nucleotides in patients with acute infections, namely pneumonia, both by the microbiological assay method. Kohn and Bernheim[4] found that all but one of their patients with pneumonia had high blood values several days after admission to the hospital. However, all patients had been on sulfapyridine therapy for several days prior to the determination and the question arises as to whether their test organism, *Hemophilus para-influenzae*, may have utilized sulfapyridine for its growth so that erroneously high blood levels of pyridine nucleotides resulted. In the present study some of the patients received antibiotic therapy with penicillin or oxytetracycline but the results of the blood level determinations bore no relation to this therapy.

Vilter *et al.*[5] reported a striking decrease in pyridine nucleotides in the blood in 17 of 20 patients with pneumonia prior to therapy. Within 24 to 48 hours after the crisis, following therapy with serum or sulfapyridine, the blood concentrations rose to normal levels in 11 of these 17 patients. These findings are consistent with the results reported in the present investigation. It is therefore possible that further studies of nicotinic acid metabolism in acute infectious diseases may reveal an explanation for the altered skin response to the tetrahydrofurfuryl ester of nicotinic acid in these states.

Summary. In acute inflammatory diseases, the application of an ointment containing an ester of nicotinic acid to the skin usually fails to produce the normal reaction of erythema. An explanation for this was sought by the measurement and correlation of nicotinic acid blood levels by the microbiological assay method with the type of skin response.

The nicotinic acid blood level varies within wide limits in normal individuals and, in a series of patients with acute infectious diseases, no correlation was seen between the nicotinic acid blood level and the type of skin response to nicotinic acid ester ointment. However, serial determinations suggested that in patients with acute infections, the blood concentration of nicotinic acid tends to rise within the normal range as the disease subsides. This may be a clue to a disturbance of nicotinic acid metabolism which may be revealed by further studies and other approaches to the problem.

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SUMMARIO IN INTERLINGUA

Le Relation Inter Nivellos Sanguinee de Acido Nicotinic e le Responsa Cutanee a un Unguento de Ester de Acido Nicotinic

In acute morbos inflammatori, le application cutanee de un unguento que contine un ester de acido nicotinic non resulta usualmente in le normal reaction erythematic. Un explication de iste phenomeno esseva cercate per medio del mesuration del nivellos sanguinee de acido nicotinic, usante le methodo del essayo microbiologic, e le correlation de ille nivellos con le typo de responsa cutanee.

Le nivello sanguinee de acido nicotinic varia grandemente in individuos normal, e in un serie de patientes con acute morbos infectiose nulle correlation esseva constatate inter le nivello sanguinee de acido nicotinic e le typo de responsa cutanee a unguento de ester de acido nicotinic. Tamen, determinationes in serie pareva indicar que in patientes con acute infectiones le concentration sanguinee de acido nicotinic tende a montar intra le limites normal quando le morbo recede. Isto es possibilemente un indication del presentia de un disturbate metabolismo de acido nicotinic. Il es a sperar que le problema va esser clarificate per studios additional e nove methodos de investigation.

SUMMARIO IN INTERLINGUA

(See page 1 for original article)

Studios Super N-Allylnormorphina in Humanos: Antagonismo a Morphina e Heroina e Effectos de Mixturas de N-Allylnormorphina con Morphina

1. In ex-morphinomanos, le administration subcutanee de n-allylnormorphina (NAM) in doses de 3, 6, e 10 mg causava un reduction del temperatura corporee e un depression del volumine-minuta del respiration que correspondeva approximativemente al effectos de 30 mg de morphina. Le resultante constriction pupillari esseva leve. Il non occurreva ulle effectos significative super le pulso e le velocitate respiratori o super le pression sanguinee.

2. Quando NAM in doses de 3, 6, o 10 mg esseva administrate simultanemente con 30 mg de morphina, o quando 10 mg de NAM esseva administrate un e tres quarte horas post 30 mg de morphina, le effectos "euphoric" e miotic del morphina esseva blocate o reducite. Del altere latere, nulle effecto antagonistic resultava super le depression del temperatura corporee e del volumine-minuta del respiration.

3. Le administration de 10 mg de NAM simultaneemente con 10 mg de heroina resultava in un effecto antagonistic super le action miotic del heroina sed non super su action depressive super le respiration.

4. Le administration oral de NAM esseva etiam efficace, sed le doses requirite esseva multo plus grande.

CLINICAL EVALUATION OF DIURETIC MERSOBEN*‡

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The effectiveness of mercurial diuretics in the treatment of congestive heart failure has been well established. By inhibiting the re-absorption of salt by the renal tubules, they promote loss of edema fluid, with corresponding diuresis, loss of body weight, and clinical improvement. Because of potentially toxic action on the kidneys and heart, recent search for mercurials with minimal toxicity and greater potency has been made. One of the more promising of these is Mersoben. This is an aliphatic compound, 3-(2 Hydroxy-3 [-D-*gluco*-pentahydroxyhexyl-mercaptomercuri]-propyl)-D-mannitol, dispensed as a lyophilized, white, amorphous, hygroscopic solid in 2 ml. vials, which is readily dissolved in distilled water immediately before intramuscular or subcutaneous injection. Preliminary studies on the dog, rat and rabbit[1] have shown favorable acute, chronic and tissue-toxicity tests.

Materials and Methods. Eighty-five patients were given single injections of Mersoben to determine the diuretic action and side effects of this experimental drug. Practically all of these patients were chronic cardiac cases who had been receiving Mercuhydrin by injection once or twice weekly for many weeks prior to the administration of Mersoben. Materials included vials of Mersoben with 175 mg. of total compound (50 mg. of mercury) hereafter designated as Mersoben 175, and vials with 140 mg. of compound (40 mg. of mercury) hereafter designated as Mersoben 140. Two milliliters of sterile water were added to each of these vials immediately prior to injection.

Additional injections were given to check for unfavorable side effects of the drug.

The mercury content of the organs of an additional 15 necropsied patients who had received Mersoben and Mercuhydrin was determined by the method of Butt and Simonsen[2].

Another drug for comparison was Mercuhydrin (meralluride sodium solution). Each ml. of this contains, in aqueous solution, 88 mg. of the sodium salt of meralluride (methoxyoximercuripropylsuccinylurea), which has 39 mg. of mercury in organic combination, and 48 mg. of theophylline. All injections were intramuscular, in 2 ml. amounts.

Subjects were all inpatients, with a variety of diagnoses. Their ages ranged from 17 to 77 years. All were kept under essentially unchanging conditions of activity, diet and medications except for diuretics during the

*Mersoben (compound Su–1775, Ciba) was kindly provided by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

‡The tissue arsenic determinations were made possible by the Spectrographic Laboratory at the Los Angeles County Hospital, which is under the direction of E. M. Butt, M.D., Chief Pathologist, Los Angeles County Hospital; and Professor of Pathology, University of Southern California, School of Medicine.

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study. They were divided into three groups: (1) Sixty-two patients were each given one injection of Mersoben 175. Nine of these had edema, the rest did not. (2) Twenty-three patients were given one injection of Mersoben 140. All of these had edema initially. Members of this group were observed most closely for changes possibly attributable to the diuretic agent, such as response of edema, blood pressure change, urinalysis preceding and subsequent to the injections, and determination of serum and urine sodium and chloride. (3) Thirty-two patients were given 58 injections of Mercuhydrin. Twenty-two of these had edema. Most were observed closely regarding the variables described for Group 2. Some of these were also given Mersoben at different times for comparison.

For all three groups the criteria for judging efficacy of the diuretic agent was weight loss of over 3 pounds, 24 hours subsequent to the administration of the drug.

For 3 to 6 days preceding injection, and 1 to 3 days afterward, daily records of the body weight (as well as diet, activity, digitalis and other treatments) were kept. Local and systemic reactions were checked in all patients.

In addition, the uptake of mercury in tissues after Mersoben injections, has been determined as an index of its toxicity. Fifteen terminal-appearing patients with severe cerebrovascular accidents, or metastatic carcinoma, who had no history of mercury-exposure, were given Mersoben 140, 2 ml. intramuscularly, and were examined post mortem for mercury content of liver, kidney, heart, brain, lung and spleen at various intervals between injection and death. Control groups of (a) 15 patients receiving known amounts of Mercuhydrin, and, (b) 50 patients with no mercurial injections, were similarly studied. The method of determination of mercury in tissues is that of Simonsen[3], in which organic matter is removed and mercury is converted into divalent form, which forms a dithizonate complex and is estimated colorimetrically. The latter is done by a Coleman Junior Spectrophotometer, in which as little as 0.2 micrograms of mercury can be detected.

Results. In the group of 62 patients, who each received Mersoben 175, 28 lost over three pounds within 24 hours following the injection, while in Group 2, which consisted of 23 patients with edema, there was a significant weight loss in 15.

In this group changes in specific gravity of urine, after injections, were observed in a few subjects, and it showed a decrease in almost all cases. There were no detectable short- or long-term blood pressure changes, and there was no urinary indication (albumin, cells, casts) of renal damage. Ten patients provided data on urine electrolyte changes following one injection of Mersoben 140. All of these had greater excretion of sodium and of chloride in the 24-hour period after injection, as compared to the previous level.

Group 3 consisted of 32 patients who received 58 injections of Mercuhydrin. Twenty-two of these were edematous. There were 47 injections in which adequate weight data were obtainable; 20 of these caused a weight loss of over three pounds within 24 hours after the injection.

The diuretic had been given to non-edematous patients as well as those with edema in order to check side effects, as well as their roughly-comparable diuretic responses. Patients with edema responded better than those without, as would be expected.

Also relevant is the effect of previous mercurial diuretics on the response to Mersoben and Mercuhydrin. Almost all of the edematous patients in our series had previously received Mercuhydrin, some weekly or twice weekly, for many months. This apparently makes it difficult for successive mercurials to be effective. It follows, that the responses to Mersoben would have been greater had untreated cases been used. In our series, responses were better when patients had had no previous treatment. We have also observed that in 30 patients, receiving both drugs, if a patient responded to Mercuhydrin, he responded to Mersoben.

Unfavorable reactions occurred rarely among a total of 132 patients who

received 142 injections of Mersoben, most being mild and none requiring treatment. Four complained of local pain or "burning" lasting a few minutes to an hour. Inspection of all injection sites after 24 hours, revealed no instance of gross irritation. Systematic reactions occurred in 7 young women of whom 3 developed mild generalized skin rash, 3 had nausea and vomiting, and one complained of crampy abdominal pains for a 2- to 3-hour period. Examination of the urine for albumin and cellular elements in most patients of Group 2 and some of Group 1, revealed no change over several days. No effect on blood pressure was apparent. A few patients developed "low salt syndrome" when given several injections of mercurials, and it was felt that this should be guarded against when using Mersoben as for any mercurial diuretic. Moderate local pain was observed in about as many patients receiving Mercuhydrin; none complained of generalized effects.

Mercury-uptake in the organs of 15 terminal patients who received no mercury other than one injection of Mersoben intramuscularly, is compared in Table 1 with that in patients who received Mercuhydrin and those without mercury-exposure. Intervals between administration of Mersoben and death, ranged from 2¼ hours to 29 days. Nine received Mersoben 175, and six received Mersoben 140. The kidney is seen to deposit more of the mercury than the other organs, and the liver next. Arbitrarily dividing the cases into 2 groups, under and over 3 days between injection and death, there appears no remarkable difference in mercury contents of any of the 6 organs. One case is excluded from the calculated averages since an especially short interval of 2¼ hours between injection and death, gave a transient high level, that is, 3.720 mg. per 100 gm. kidney, 0.904 mg. liver, 1.330 mg. heart. One

TABLE 1.—MERCURY CONTENT OF VARIOUS ORGANS AFTER MERSOBEN, MERCUHYDRIN, AND WITHOUT HG-EXPOSURE

Drug	*Number Points*	*Av. Interval Inj.–Death*	*Years Av. Age*	*Average Hg mg./100 gm. Dry Tissue*					
				Liver	*Kidney*	*Heart*	*Brain*	*Lungs*	*Spleen*
Mersoben 2 ml. (under 3 days before death)	5	38 hours	60	0.242	1.282	0.084	0.083	0.073	0.059
Mersoben 2 ml. (over 3 days before death)	9	9 days	64	0.059	1.556	0.050	0.072	0.077	0.083
Mercuhydrin 2 ml. (within 2 wks. before death)	6	6 days	61	0.35	2.90	0.16	0.04 (2 cases)	0.14 (2 cases)	0.27 (2 cases)
Pts. on Merc. for C.H.F. (Butt & Simonsen)[5]	22	Variable intervals and amounts	58	3.028	34.473	...	...	...	...
No known Hg	30		63	0.012	0.376	0	0.040	0	0
No known Hg (Butt & Simonsen)[5]	34		29-80	0.076	0.316	...	...	...	...

case of Mercuhydrin injection one hour before death, without previous mercurials, showed 15.9 mg. per 100 gm. kidney; this was also omitted from the averages.

Comparing the mercury levels following one 2 ml. injection of Mersoben, with those following a similar volume of Mercuhydrin, it is seen that the former values are lower for all organs except the brain. The small number of cases probably causes inaccuracies in the ratios. Mercury contents with somewhat larger amounts, 2 to 14 ml., of Mercuhydrin, are, in general, slightly greater but still insignificant in terms of toxicity. Patients on mercurial diuretics (Mercuhydrin in all cases) for varying lengths of time, as described by Butt and Simonsen, using the same techniques, are shown to have much higher values of mercury in their livers and kidneys. Some individual records show kidney, for example, to contain over 60 mg./100 gm. wet tissue. Finally, it must be pointed out that patients without any form of mercury intake, may be found with some measurable amount of this trace element. Our averages from 50 cases are comparable to those of Butt and Simonsen[2].

Discussion. An incomplete study of this nature is presumptive rather than final evidence that a new diuretic can find a favorable place among several established ones of similar mode of action. Much that has been left undone would still be pertinent and interesting, such as the repeated use in chronic patients, or intravenous use in more urgent situations. We have not used Mersoben in children, or in patients with renal disease. Apparent advantages of Mersoben are: 1) Its potency as a diuretic, plus 2) its small amount of mercury hence, presumably, minimal toxicity.

The work of Butt and Simonsen[2] indicates that "large amounts of mercury may be present in human tissues without histologic evidence of functional alteration." Forney and Harper[3] found no microscopic evidence of the pathologic changes associated with acute mercury poisoning in kidneys and livers which had higher mercury contents than our Mersoben patients. Such an advantage may be emphasized when many injections are necessary over long periods in chronic congestive failure patients. The work of Baxter[1] is in general agreement with ours regarding the effectiveness as well as toxicity of Mersoben (Su–1775). They observed, in addition, no pathological nonprotein nitrogen rise.

Summary and Conclusions. 1. Eighty-five patients were given single injections of Mersoben to test its diuretic activity.

2. Mersoben is a potent diuretic and it has the advantage of containing a relatively small amount of mercury.

3. Side effects of Mersoben are minimal with the doses described. We have seen no evidence of local, renal, or systemic ill effects, except infrequent local pain and rare sensitivity reaction.

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(Interlingua on page 50)

TREATMENT OF PEMPHIGUS WITH POTASSIUM PARA-AMINOBENZOATE

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Prolonged administration of large doses of potassium para-aminobenzoate (KPAB) has been shown to be bene-beneficial in a variety of clinical disorders[5,11,13,16-23]. Favorable results in dermatitis herpetiformis[21] suggested a trial of KPAB therapy in another bullous condition, namely, pemphigus. Accordingly, the present study was begun in January, 1949, prior to the introduction of cortisone and ACTH. While these studies were underway, therefore, the hormonal compounds were shown to effect prompt and dramatic improvement in many subjects with this disorder. However, experience has shown that the disease is not always completely suppressed by treatment with cortisone or ACTH[6]. Furthermore, long-range high-dosage hormonal therapy is often accompanied by serious toxic effects which may interrupt or preclude their use[6,7,9]. For these reasons, it is believed that the following observations concerning the treatment of pemphigus with potassium para-aminobenzoate may be of interest at this time. In addition, attention will be drawn to the combined use of KPAB and steroid therapy in severe cases of pemphigus.

Material and Methods. Eighteen patients with various forms of pemphigus have been treated during the past six and one-half years. Twelve were studied at the hospital of the University of Michigan, and six at the Temple University Hospital. All of the cases were diagnosed by members of the dermatologic services of the respective institutions. Classified into clinical types after the criteria of Ormsby and Montgomery[8], there are 10 cases of pemphigus vulgaris, 4 cases of pemphigus foliaceus, 3 cases with pemphigus erythematodes, and 1 case of ocular pemphigus.

Potassium para-aminobenzoate (KPAB) was administered as a 10% aqueous solution, usually 30 ml. (3.0 gm.) every 3 hours for 6 to 8 doses daily; that is, a total of 18 to 24 gm. of KPAB per day. Our patients have preferred the liquid to the tablet form of medication. Pure, prescription grade KPAB*, 100 gm. in one quart of water, gives an easily prepared solution of satisfactory concentration for clinical use. The solution should be stored at refrigerator temperature, protected from ultraviolet light and administered chilled.

Although KPAB is much better tolerated than para-aminobenzoic acid or its other salts, some sodium para-aminobenzoate was used when KPAB was in short supply.

Aside from the relatively high dosage

*Much of the potassium para-aminobenzoate (POTABA) administered to these patients was generously contributed by the Glenwood Laboratories, Teaneck, New Jersey.

schedule, the most important requirement of KPAB therapy in these patients was that of prolonged administration. This and other aspects of KPAB treatment will become evident from the brief case histories which follow.

Case Reports. PEMPHIGUS VULGARIS. *Case 1.* S. Z., a 66-year-old Syrian woman, was admitted to the University of Michigan Hospital on November 23, 1949, complaining of a skin eruption. She had developed a sore throat in early spring of 1949, followed by sores on the roof of the mouth. These lesions were resistant to local therapy. In October, 1949, large blisters appeared on the right arm and shoulder. During subsequent weeks many more bullae formed over the body. The bullae increased in size, ruptured, and left painful denuded areas.

The physical findings were largely confined to the skin, where an extensive bullous eruption was seen over the entire body except for the scalp, palms, and soles (Fig. 1*a*, *b*). The mucous membranes of the mouth were also involved.

Initial therapy consisted of pyribenzamine, sulfadiazine, and aureomycin. However, there was constant formation of new bullae. Potassium para-aminobenzoate, 18 gm. daily, was started on December 2, 1949, and within 2 weeks no new lesions were noted. The administration of KPAB was continued until January 20, 1950, at which time she was completely free of lesions and showed only residual hyperpigmentation (Fig. 1*c*, *d*).

Following cessation of KPAB therapy, the patient remained in clinical remission for 7 months; then in August, 1950, the bullous eruption reappeared. She was readmitted in September and was given cortisone. New lesions continued to appear during the next 3 months despite steroid therapy.

Case 2. H. W., a 55-year-old white housewife, was admitted to the University of Michigan Hospital on March 13, 1950. She had been well until the latter part of December, 1949, when she noted the onset of scattered bullous lesions on the abdomen. These appeared to arise in normal skin. Gradually involvement extended to the patient's face, back, arms and legs. The eruption had become progressively worse despite numerous forms of therapy.

Examination revealed the temperature to be 101° F., the pulse 95 per minute, and respirations 24 per minute. A generalized, flaccid bullous eruption was present, with greater concentration of lesions on the scalp, in the axillae, under the breasts, about the umbilicus, and about the inguinal regions (Fig. 2*a*, *b*). Many of the lesions had ruptured. Two small denuded areas were noted on the buccal mucosa. There were also areas on the soft palate beneath the tongue. A small conjunctival ulcer was present in each eye. Except for moderate bilateral cervical lymphadenopathy, the remainder of the physical examination was within normal limits.

Routine blood and urine studies were negative except for a leukocytosis of 14,400 per c.mm. The serum proteins totalled 5.5 gm. %, with 2.8 gm. albumin and 2.7 gm. globulin. The gamma globulin value was 8.8 units.

The diagnosis of pemphigus vulgaris was made. The patient was placed on a regimen of 400,000 units penicillin daily, potassium permanganate baths daily, and 2% gentian violet to the denuded areas. After the initial studies were completed, potassium para-aminobenzoate therapy was begun at a schedule of 21 gm. daily. Gradually, the patient became afebrile, the lesions improved markedly (Fig. 2*c*, *d*), and she was discharged on April 21, 1950, to continue KPAB treatment at home. While at home, she got along well except for weakness and occasional mental aberrations. On May 2nd, she became somewhat confused and had complete anorexia. The KPAB was continued, however, until May 4th when she was more confused and thrashed about in bed. Her local physician administered morphine and phenobarbital hypodermically, following which she became comatose and was re-admitted to the hospital on the same day.

Examination revealed the patient to be comatose. The skin was dry, and there were some crusted, healing areas on the trunk. However, there were no new vesicles or bullae. The pupils were pin-point in size, and fixed to light.

The blood sugar value on admission was 7 mg. per 100 ml., and the CO_2 combining power 41 vol. %.

The admission diagnosis was hypoglycemic coma, enhanced by morphine and phenobarbital. Intravenous glucose was administered and it was possible to rouse the patient after 24 hours. Despite normal blood sugar and electrolyte values, however, the patient remained somewhat irrational. Numerous vesicles began to appear on the trunk and extremities about 2 weeks after the KPAB had been discontinued. This was believed to represent a relapse of the pemphigus. The patient was discharged on May 20th to be followed in the outpatient clinic.

By June 8th, the eruption had become generalized, and it was decided to resume KPAB therapy as the patient was oriented and the drug was to be administered by her

daughter only if an adequate dietary intake were maintained. Over the next 3 weeks, however, numerous new bullae appeared and the patient was again admitted to the hospital on June 29, 1950. KPAB was continued until July 13th when it was stopped because the fasting blood sugar had fallen to 35 mg. At the same time, however, she had been receiving penicillin and sulfadiazine for secondary skin infection. On July 22nd, cortisone therapy was instituted at 100 mg. daily and continued to August 16th without benefit. The patient's condition continued to deteriorate and she expired on August 31, 1950.

Case 3. A. C., a 95-year-old widow, entered the University of Michigan Hospital on March 3, 1950, complaining of blisters on her skin since December, 1949. In May, 1949, she had developed a sore mouth which was due to the presence of a "canker sore." This was slow in healing and the patient was not free of oral symptoms until August. Four months later, a blister appeared on the right thumb, extending from the nail to the base. Gradually, the arms and chest became involved with bullae. These lesions were pruritic, would break and crust, then finally disappear. Treatment had consisted of ointments and various pills of unknown composition. The systemic review elicited a history of episodes of cardiac palpitation and dyspnea, and occasional ankle edema. She also had urinary frequency (10 to 15 per day) and nocturia, 2 to 3 times. Past history included an operation for the removal of breast cancer 6 years prior to this admission.

Examination disclosed an elderly woman who was not acutely ill. Many large, clear bullae were seen over the chest, arms, hands, abdomen, and the legs. Some of these were broken, revealing a red, denuded, weeping surface. There were bullae and erythematous patches on the oral mucous membranes. Coarse moist rales were heard at both lung bases. Examination of the heart revealed a grade II systolic murmur at the apex. Occasional extrasystoles were heard. The liver was palpable 2 fingers breadth below the right costal margin. There was no peripheral edema.

The admission urinalysis and blood count were within normal limits. The total serum proteins were 6.5 gm. per 100 ml., with 3.4 gm. albumin and 3.1 gm. globulin. The gamma globulin determination was 19.0 units.

On March 8th, the patient was started on KPAB, 7 gm. per day, and this was increased to 21 gm. daily over the next 2 days. During her hospitalization, she was also treated locally with potassium permanganate baths. In addition, the patient was given 50 mg. pyribenzamine, q.i.d., for pruritus, and injections of penicillin to combat secondary infection.

She was discharged on March 15, 1950, with the recommendation to continue taking KPAB. Two weeks later, the patient's family returned to the Outpatient Department to state she was doing well as far as her skin was concerned, but that her appetite was poor. It was advised that the administration of KPAB be interrupted until her appetite returned. On July 8, 1950, the patient's son stated that she was doing very well on KPAB and had only one lesion.

A note was later sent to the hospital that the patient had expired on August 17, 1950. Correspondence with her referring physician indicated that death was probably due to old age.

Case 4. J. K., a 59-year-old white male clothier, was admitted to the University of Michigan Hospital for treatment of a bullous eruption which had been present for 6 weeks. Lesions first appeared on the back of the head, about the nares, lips, and on the oral and nasopharyngeal mucous membranes. At the time of admission, there was a bullous lesion on the left shoulder, and an extensive bullous erosion of the perineum. The patient appeared toxic. His diagnosis was acute pemphigus vulgaris. Aside from local therapy, he was given KPAB, starting with 8 gm. on February 10, 1949, and 16 gm. daily for 2 weeks. As there was no evident improvement at the end of 2 weeks of treatment, KPAB was discontinued and arsenical therapy was instituted. The patient expired about 2 months later.

Case 5. G. L., a 44-year-old colored female, was admitted to the University of Michigan Dermatology Service on March 7, 1950. She complained of skin trouble of one year's duration. Initially, small blisters appeared on the hands, but within 2 months similar lesions involved the entire body. Oral lesions were also present, making it difficult for her to swallow. There was no history of drug ingestion prior to the eruption. Despite various medications, she became progressively worse and was advised to enter the hospital. The past history was noncontributory.

Examination revealed the patient to be emaciated. A bullous eruption was present over the entire body except for the scalp. The intact bullae were flaccid, while the ruptured lesions disclosed an erythematous weeping base. Depigmented areas were seen as evidence of healed lesions. The remainder of the examination was negative.

Laboratory studies revealed the hemoglobin to be 8.8 gm., and the leukocytes

numbered 10,300 per c.mm. with a normal differential. Urinalysis was negative. The serum proteins totalled 8.6 gm. %, with 3.5 gm. albumin and 5.1 gm. globulin. The gamma globulin determination was 40.6 units.

On March 9, 1950, the patient began to receive KPAB in gradually increasing doses to 21 gm. per day by March 12th. She developed slight nausea on the seventh day of drug administration, necessitating temporary decrease in the dosage. However, by March 24th the drug had again been increased to 21 gm. daily. The skin lesions responded slowly; occasional new bullae were seen, and there continued to be bleeding from several denuded areas. Repeated blood

Fig. 1*a* and 1*b*.—Pemphigus vulgaris Case 1 (S. Z.) as she appeared on December 2, 1949. Fig. 1*c* and 1*d*.—Same patient on February 13, 1950, after 10 weeks of KPAB therapy.

transfusions were required to maintain the hemoglobin level. The KPAB was discontinued on April 13th due to a recurrence of nausea and vomiting, but by April 17th, therapy was resumed with no further distress. Definite but gradual improvement of all skin lesions was seen over the next 4-month period. There were observed no new bullae during the last month of treatment. She was discharged, ambulatory, on September 10, 1950, and was therefore hospitalized. The remainder of his history was noncontributory.

On examination, the patient was afebrile. There were numerous ruptured and intact flaccid bullae over the face, neck, chest, back, abdomen, arms and genitalia. The lower extremities were relatively clear. The tongue and mucous membranes of the mouth were involved with lesions which left denuded areas. Nikolsky's sign was not elicited. The

Fig. 2*a* and 2*b*.—Pemphigus vulgaris. Case 2 (H. W.) photographed on March 15, 1950.
Fig. 2*c* and 2*d*.—After 2 months of treatment with potassium para-aminobenzoate.

was advised to continue KPAB, 18 gm. daily, at home.

Case 6. C. H., a 54-year-old colored foundry worker, was admitted to the University of Michigan Hospital on March 9, 1950. He had been well until 4 weeks prior to admission at which time his mouth became sore and he noted a blister on the left naris. Scattered bullae then appeared on other parts of the body. Despite local therapy he continued to develop skin and oral lesions and remainder of the physical examination was within normal limits.

The admission urinalysis was negative. The hemoglobin was 11 gm. %, but the other routine blood studies were normal. Serum proteins totalled 7.7 gm. %, with 3.6 gm. albumin and 4.1 gm. globulin. The gamma globulin determination was 29.2 units. The fasting blood sugar was 72 mg. per 100 ml., and a test for plasma ascorbic acid detected none of this vitamin.

Treatment consisted of local measures including potassium permanganate baths (1:30,000) twice daily; 1% aqueous gentian violet to all skin lesions; elixir of benadryl mouth wash 3 times daily, before meals; and the patient was placed in a starch bed. He continued to develop more lesions, however, and his condition deteriorated progressively. Penicillin, 400,000 units, twice daily, and KPAB up to 18 gm. daily were added to his program. On March 21st, he developed

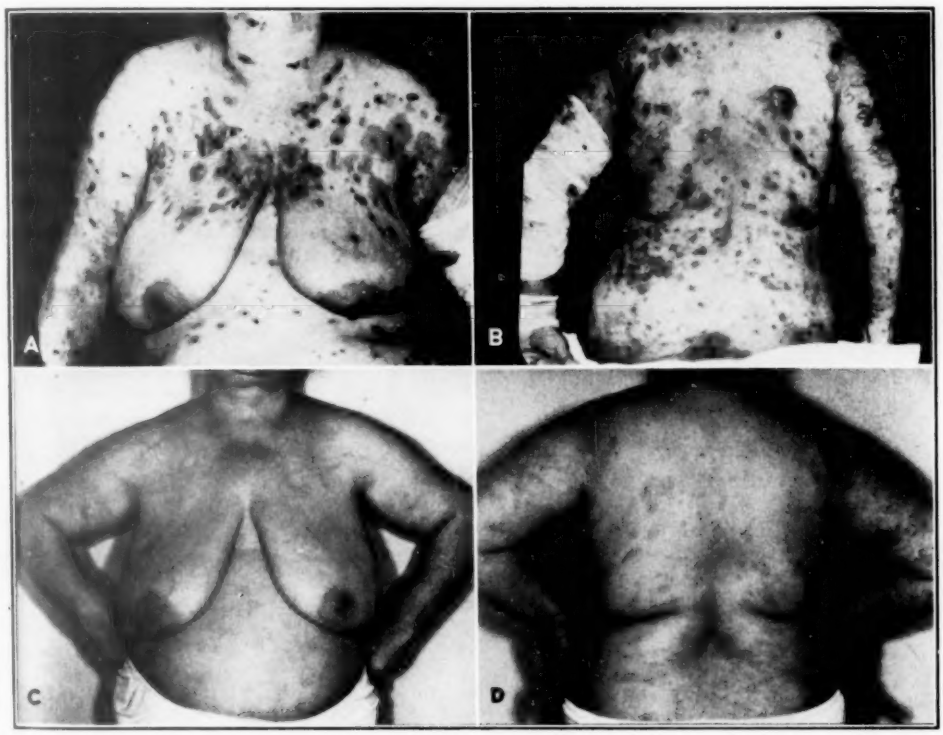

Fig. 3*a* and 3 *b*.—Phemphigus vulgaris. Case 7 (M. T.) on November 3, 1951.
Fig. 3*c* and 3*d*.—Show patient on June 27, 1952, with complete suppression of the disease process by KPAB treatment.

singultus, and was able to take very little oral medication or nourishment so that the KPAB was stopped. Ten days later the patient expired.

Case 7. M. T., a 56-year-old Syrian woman, was admitted to the Temple University Hospital on October 29, 1951, complaining of a skin eruption. She had been asymptomatic until 7 months prior to admission when bullae appeared about the buttocks and genitalia. Gradually the eruption became generalized. A dermatologist was consulted and he made a tentative diagnosis of dermatitis herpetiformis. Sulfapyridine and Fowler's solution were each given short trials without improvement, and the eruption continued to grow worse until the time of admission. Aside from the present illness, the only pertinent aspect of her history was that she had been known to have high blood sugar levels.

Examination revealed an obese woman in obvious distress. There was a generalized eruption characterized by numerous tense bullae, superficial weeping areas, and some crusted and scarred lesions of apparently longer duration. Lesions were also present in the nose and mouth. The Nikolsky sign was not elicited. However, the clinical diagnosis was pemphigus vulgaris.

The admission urinalysis was negative. Other studies were deferred because of the extensive eruption.

In view of the history of elevated fasting

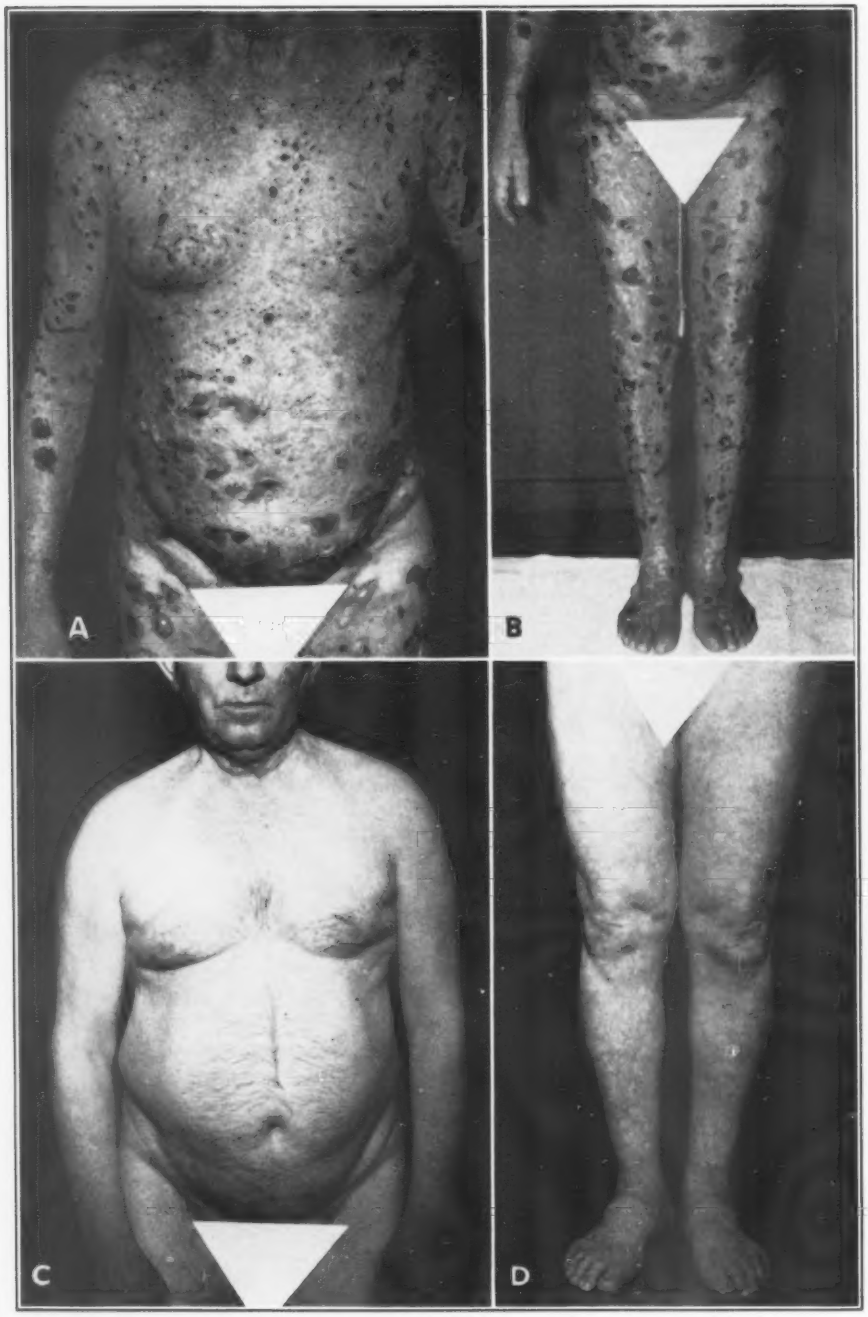

Fig. 4*a* and 4*b*.—Pemphigus vulgaris. Case 9 (G. G.) as he appeared on December 7, 1953.
Fig. 4*c* and 4*d*.—Complete suppression of the disorder was achieved and maintained with combined KPAB and cortisone treatment. Photographs taken July 21, 1955.

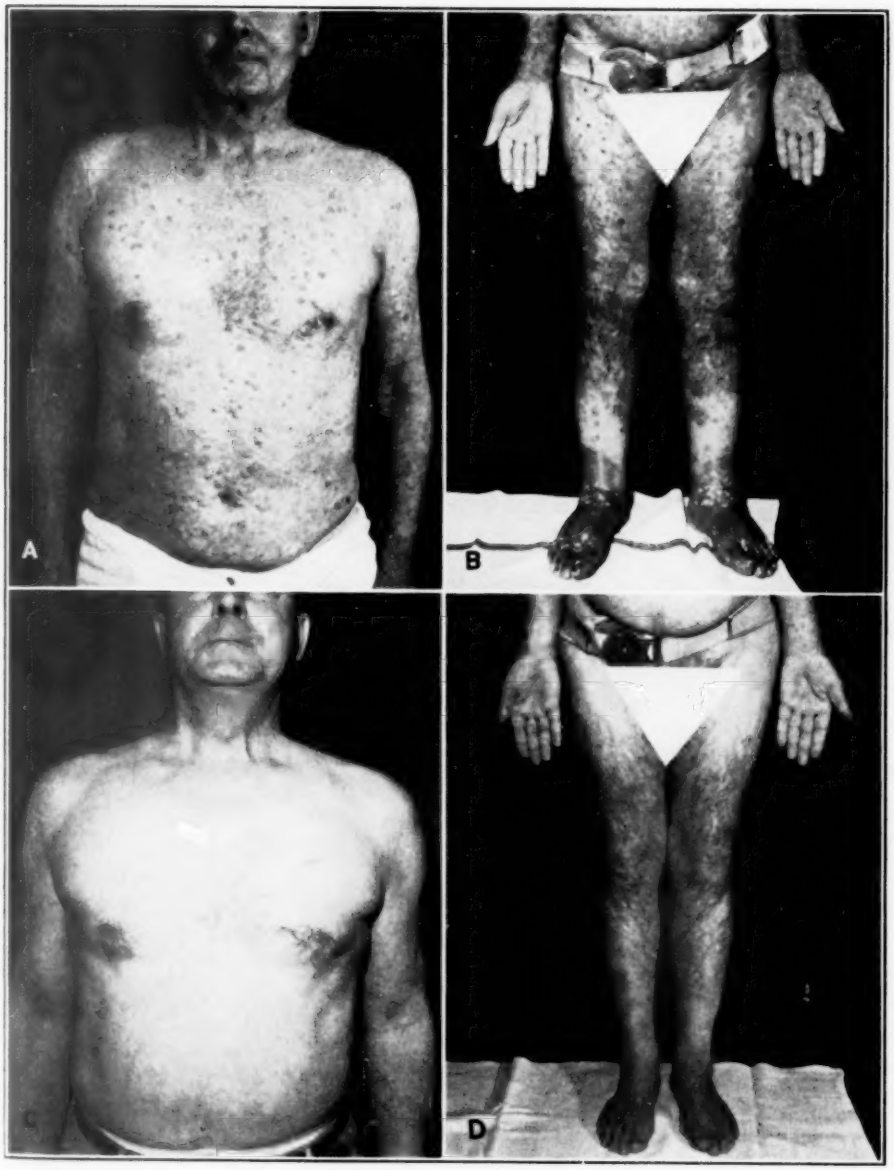

Fig. 5*a* and 5*b*.—Pemphigus vulgaris. Case 10 (W.L.) on September 9, 1954.
Fig. 5*c* and 5*d*.—Remission resulted from combined Potaba and cortisone therapy as is evident from the photographs taken September 10, 1955.

blood sugar levels, cortisone was deferred in favor of KPAB therapy which was begun on November 3, 1951 (Fig. 3*a*, *b*). The patient received 2 gm. every 3 hours for one day, then 3 gm. every 3 hours (24 gm. daily). Within a week there was considerable decrease in exudation and beginning of healing of lesions was evident. The patient was discharged on November 11th to continue on KPAB therapy as an outpatient. After a few days, the dosage schedule was changed to 4 gm. KPAB every 3 hours during the day only. Blood studies on November 17, 1951, showed the hemoglobin to be 12 gm. %, the hematocrit 37%, and the leukocytes numbered 6,900 per c.mm. The fasting blood sugar level was 131 mg.

Therapy was well tolerated and gradual improvement followed, so that by the end of November, 1951, the patient was able to return to her home in Tucson, Arizona. Although occasional small vesicles were noted, the patient was progressively more comfortable, gradually regained strength and weight, and resumed activity. By the end of February, 1952, new bullae no longer appeared and there remained only pigmentary changes. KPAB, 24 gm. daily, was continued for several months, however, in order to maintain suppression of the process (Fig. 3*c*, *d*). The KPAB dosage was then gradually reduced and then omitted entirely in February, 1953. There was no evidence of relapse up to one year later when the patient was last heard from.

Case 8. D. K., a 69-year-old white male, was admitted to the Temple University Hospital on June 20, 1952, complaining of blisters all over his body. The patient had been well until April, 1952, when scattered bullous lesions first appeared. These were pruritic, would rupture easily, and new lesions continued to appear as older ones became crusted. Therapy prior to admission had consisted only of local applications of calomel lotion.

Fig. 6*a*.—Pemphigus foliaceous. Case 2 (J. A.) as he appeared on September 22, 1949, at the time potassium para-aminobenzoate administration was begun.
Fig. 6*b*.—Same patient on June 7, 1950. Note partial suppression of the disease, including some regrowth of hair.

Examination revealed bullous lesions on the scalp, face, thorax, abdomen, arms and legs. The Nikolsky sign was absent. (There were no mucous membrane lesions at the time of admission but oral lesions were observed during the next 4 weeks.) Except for slight enlargement of the liver and bilateral inguinal hernias, the remainder of the physical examination was negative.

Laboratory examinations revealed the hemoglobin to be 12.5 gm. %, the hematocrit 42%, and the leukocyte count was 7,700 per c.mm. Urinalysis was negative. The serum albumin was 4.0 gm. %, and the globulin was 2.0 gm.

The patient was started on KPAB therapy on June 29, 1952. He received 7 doses of 2

gm. each the first day, and 7 doses of 3 gm. daily thereafter. There was gradual improvement, but new vesicles were still appearing on July 14th, when he was discharged from the hospital to continue KPAB at 21 gm. daily. Therapy was well tolerated and the patient was free of lesions by September 15th. The dosage of KPAB was lowered to 18 gm. daily over the next 4 weeks, and then reduced to 15 gm. daily (5 × 3 gm.) for 2 weeks, and then to 12 gm. daily for 4 weeks. As there was no evidence of recurrence, the administration of KPAB was stopped on November 21, 1952. The patient has remained in remission to date.

Case 9. G. G., is a 64-year-old waiter of Greek extraction whose pemphigus vulgaris began in February, 1953. He first consulted Dr. Carroll S. Wright in June, 1953, at which time he exhibited a multiform generalized

Fig. 7*a* and 7*c*.—Pemphigus erythematodes. Case 1 (G. B.) as he appeared on December 2, 1949, prior to the institution of KPAB treatment.

Fig. 7*b* and 7*d*.—Photographs of March 17, 1950, reveal remission achieved. (Vertical lines on neck and abdomen are artefacts.)

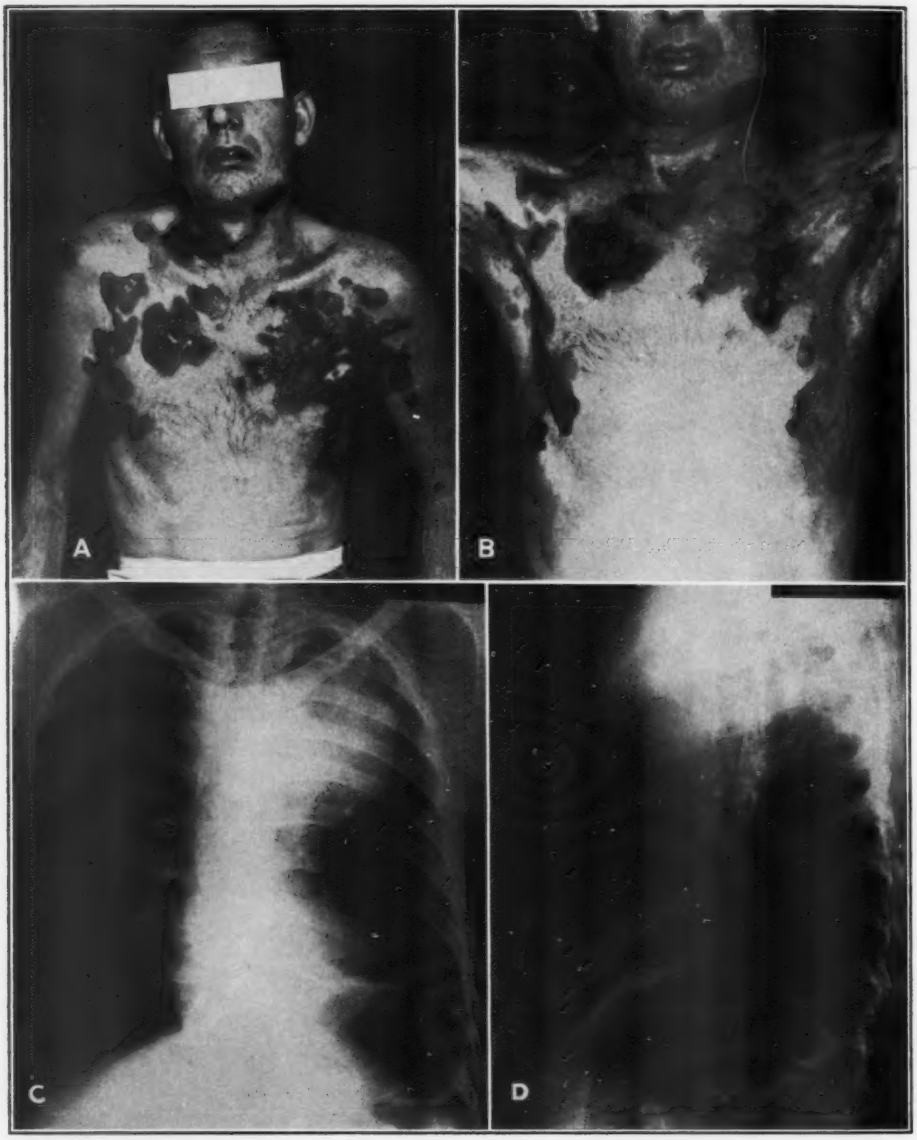

Fig. 8*a*.—Pemphigus erythematodes Case 3 (J. G.). Baseline photograph taken January 26, 1955, at the time combined Potaba and cortisone therapy was begun.

Fig. 8*b*.—Appearance on March 23, 1955. Note improvement of skin and further enlargement of tumor mass on the face.

Fig. 8*c* and 8*d*.—Roentgenographic appearance of intrathoracic tumor mass (February 14, 1955), diagnosed as adenocarcinoma from needle-biopsy specimen.

eruption with prominent bullae up to hen's egg size. There were also denuded areas from ruptured bullae, and erythematous plaques. The mucous membranes were clear. He was first treated with 40 units of ACTH and cortisone, 100 mg. daily, in divided doses. Because of marked progression of the disease, the patient was admitted to the Skin and Cancer Hospital of Philadelphia on July 2, 1953. Sulfapyridine therapy for 10 days had no effect and new bullae continued to form. He was then given 40 units of ACTH daily, and oral cortisone, 200 mg. daily. After ... days on this program, there were no new bullae, and the patient presented healing papular areas and erythematous plaques. In addition to the cutaneous involvement, the patient had developed urinary retention, for which an indwelling catheter was worn.

He was discharged from the hospital on July 27th on a prescription containing Fowler's solution, sodium bromide, and Benadryl. Within 3 days, a generalized bullous eruption appeared, including a lesion in the left naris. Cortisone was resumed, 200 to 300 mg. daily, along with ACTH injections every few days. At times, he was almost free of lesions, but with diminishing doses, new bullae developed.

Accordingly, he was referred for possible KPAB therapy on November 20, 1953. Examination at that time revealed an extensive, generalized bullous eruption which persisted despite a treatment program consisting of 60 units of ACTH and 200 mg. of cortisone, daily. The hormonal program was discontinued and he was placed on 18 gm. KPAB, daily. Over the next two weeks, there was an exacerbation of the eruption and he was admitted to the Temple University Hospital.

The appearance of the skin at that time may be seen in the accompanying photographs (Fig. 4*a*, *b*). Aside from the presence of a moderate degree of anemia, the routine laboratory findings were negative. The blood urea nitrogen was 8 mg. per 100 ml. He was referred to an urologist, Dr. Trudeau Horrax, who noted that the prostatic obstructive symptoms had antedated the dermatologic disorder by about one year. Of unusual interest was the observation by Dr. Horrax of 2 bullous lesions in the prostatic urethra on December 18th. He advised continued catheter drainage until such time that a transurethral resection would be feasible.

In addition to the KPAB, 18 gm. daily, cortisone was begun at a schedule of 75 mg. every 8 hours, along with starch baths twice daily. Improvement was evident within a few days, with new lesions being progressively fewer and smaller. By January 5, 1954, the skin was free of lesions and prostatic resection was performed. The operation was uneventful, but a transient episode of shock occurred late the same day. In retrospect it appeared that the patient's collapse was due to inadequate cortisone during the immediate postoperative period. Oliguria was present for a few days, and there was a marked rise in the blood urea nitrogen (122 mg.) and serum creatinine (8.3 mg.). For this reason, the KPAB was omitted, and the diet was altered to contain little protein (20 gm.) and high amounts of carbohydrate and fat. Two weeks postresection, the urinary creatinine clearance test was 9.3% of normal, and the intravenous PSP excretion test yielded only 18.3% of the injected dye after one hour. Clinically, the patient remained very well. The renal tests continued to indicate marked functional impairment for 4 more weeks, and then quickly returned to normal. Accordingly, KPAB was resumed on February 26, 1954, at 1 gm. (10 ml. of the 10% solution), 6 times daily, and progressively raised to 3 gm., 6 times daily. Cortisone was decreased to 50 mg. every 8 hours and the patient was discharged from the hospital on March 11th, and thereafter followed in the outpatient clinic. His skin remained free of bullae, although the dosage of cortisone was gradually reduced to 25 mg. every 8 hours, while the KPAB was continued at 18 gm. daily. The latter was reduced to 15 gm. daily in August, 1954. In addition to the cutaneous improvement, the patient has gained over 30 pounds in weight, and he feels entirely well on the above dosage program which has been maintained for the past year. The appearance of the patient on July 21, 1955 is shown in Fig. 4*c*,*d*.

Case 10. W. L., a 64-year-old white male, first developed lesions of pemphigus in May, 1954. As the disorder progressed, he was admitted to the Skin and Cancer Hospital of Philadelphia on June 7, 1954. There he was treated with hydrocortisone, up to 320 mg. daily; ACTH in varying doses intramuscularly, and up to 25 units intravenously daily; terramycin, 250 mg., 4 times daily; whole blood transfusions; sulfadiazine; and numerous vitamin preparations and supportive measures. The bullous lesions present on admission were debrided as were new ones as they appeared. During the first 6 weeks, numerous bullae continued to form, and the patient was very ill and required constant nursing care. After changing from intramuscular to intravenous ACTH, however, and continued administration of hydrocortisone (240 mg. daily), the process gradually sub-

sided. Unfortunately, edema was prominent despite salt restriction, Diamox, and mercurial diuretics. Treatment was continued until August 16, 1954, at which time the patient was discharged from the hospital. Within 2 days, bullous lesions began to reappear and became generalized by September 9, 1954, when his local physician, Dr. Allen Beckley, referred him for treatment. The extent of recurrence, and the marked edema of the legs are evident in the accompanying photographs (Fig. 5*a, b*). The Nikolsky sign was elicited with ease. His weight was 148 pounds. (It had been 162 pounds prior to the onset of his present illness.)

Laboratory studies revealed the hemoglobin to be 11.5 gm. %, the leukocytes numbered 9,600 per c.mm. with 18.5% eosinophils.

Because of economic considerations, it was necessary to treat this patient on an outpatient basis. In view of the poor response to prior high dosage steroid therapy, it was decided to place him on a combined KPAB and cortisone treatment regimen. Accordingly, KPAB was begun, 20 ml., 6 times daily, and increased to 30 ml., 6 times daily within 4 days. Cortisone was given orally, 25 mg. every 8 hours. The salt intake was moderately restricted, but the diet was otherwise liberal. Achromycin, 250 mg. every 6 hours, was added 2 days later because of the advent of fever to 104° F. This subsided in 3 days, and the Achromycin was discontinued. New lesions continued to appear but were smaller than at the beginning of treatment. At this point, the dosage of cortisone was raised to 50 mg. every 8 hours. Within the next few days improvement was marked; he began to lose the edema fluid; lesions appeared with decreasing frequency and were progressively smaller. He became ambulatory and was able to return to work 2 months after the treatment program had been instituted. Over the succeeding months, the KPAB dosage was kept at 18 gm. daily, while the cortisone was slowly reduced. In December, 1954, he experienced an attack of herpes zoster (despite cortisone therapy), but from that time on his course was uneventful. The cortisone dosage was reduced to 25 mg. every 8 hours on February 5, 1955, and has been kept at that level to date. Aside from suppression of the cutaneous lesions, the patient's improvement has been characterized by weight gain to 162 pounds, despite loss of edema fluid, and restoration of the hemoglobin value to normal (14.9 gm. %). The Nikolsky sign remained negative. However, in May, 1955, there appeared on his chest 3 small areas about 1 inch in diameter which exhibited a few small vesicles. The treatment program, consisting of 75 mg. of cortisone and 18 gm. KPAB daily, was not altered and these areas of activity gradually subsided. The appearance of this patient after one year of combined KPAB-cortisone therapy is shown in Fig. 5*c, d*.

PEMPHIGUS FOLIACEUS. *Case 1.* S. S., a 40-year-old housewife, entered the Dermatology Service at the University of Michigan on November 9, 1948, complaining of a skin eruption of 2 months' duration. This began as an erythematous pruritic rash over the upper back. Although treated with an ointment, the process had spread to cover the anterior chest and the entire back during the next 2 weeks. There was slight vesication associated with the eruption as well as some weeping and crusting. During the week prior to admission it extended to involve the legs, scalp, and roof of the mouth. The patient gave no history of previous drug ingestion.

Examination of the skin revealed an area about 5 by 8 inches in diameter on the patient's chest which had been completely denuded. About the edges of this area were numerous vesicles and bullae and a few erythematous papules. On the upper back was an erythematous crusted eruption. Lower on her back were scattered lesions which appeared to have been bullae. A positive Nikolsky sign was present. There were a few erythematous crusted lesions on the patient's abdomen. There was a denuded area on the patient's soft palate.

Laboratory findings on admission to the hospital on the above date revealed a normal urinalysis and blood count.

The diagnosis of pemphigus foliaceus was made.

The patient had a prolonged, stormy hospital course. Many different types of therapy were attempted without benefit and the eruption became generalized. KPAB was started on January 5, 1949. She initially received 14 gm. per day and this was gradually increased to 21 gm. daily. After the institution of this therapy she began to show definite improvement, though gradual. At the time of discharge on February 27, 1949, there were scattered, irregular areas of erythema and scaling over the body surface.

She continued KPAB at home for a short while, but a consultant who was called is said to have doubted the diagnosis and stopped therapy. The patient subsequently relapsed, and then was given cortisone.

Case 2. J. A., a 49-year-old white male, was first seen in the University of Michigan Dermatology Outpatient Department in Feb-

ruary of 1942. He began having skin trouble in August, 1941, when he developed boils on the left side of the face, in both axillae, and in the scalp. These required repeated lancing. In October, 1941, he noticed the development of blisters on his wrists and legs. From that time until he was seen at the Clinic the skin had gradually become more and more involved in a process characterized by blister formation and exfoliation. He complained of no sores in his mouth or nose. The eruption was slightly pruritic.

On his first visit, examination revealed an extremely extensive eruption consisting of very shallow erosions of the skin. On the soles of both feet were small pea-sized blebs arising from normal skin. Occasional flaccid bullae were seen on the arms. The entire scalp, neck and face were involved. The Nikolsky sign was easily elicited. It was thought this patient had pemphigus vulgaris and he was admitted to the hospital and treated with wet dressings and colloidal baths. He received several blood transfusions. In conjunction with the above he began to receive stilbestrol and asiatic pills. The patient's course was stormy, and his eruption gradually changed in characteristics to that of pemphigus foliaceus. In spite of many types of local treatment, including sulfathiazole ointment, cod liver oil, chlorophyll ointment, thioglycerol, and others, his course was prolonged, with very little improvement. After an unsuccessful trial with asiatic pills the patient began to receive Stovarsol. He was discharged after 18 months in the hospital to continue taking this drug at home.

The patient returned on September 19, 1949, to re-enter the hospital. In the interim he had been in and out of other hospitals and at no time had he been free from his eruption. His examination at the time of this admission was essentially unchanged from that of the previous one (Fig. 6*a*). He began to receive KPAB on September 23rd. During the next 6-month period the patient's eruption gradually but definitely improved (Fig. 6*b*). There was much less exudation and scaling. He required occasional blood transfusions to maintain the hemoglobin level, and his chief complaint was that of pruritus. His condition became somewhat static, however, with no additional improvement over a 3-month period from June, 1950, to September, 1950. Over this entire 12-month period he received from 18 to 21 gm. of KPAB per day. The drug was well tolerated. Because of the lack of further improvement, the KPAB was discontinued on October 11, 1950, and cortisone was given, 50 mg., intramuscularly, twice daily. There followed the expected euphoria and general sense of well-being, and possibly some further improvement in the condition of his skin. The dosage of cortisone was then increased to 150 mg. daily, but this was accompanied by edema. The amount of cortisone was reduced to 100 mg. daily, with some worsening of the eruption. The patient was later placed on ACTH and local measures and remained reasonably comfortable on this program. In January, 1952, the patient was readmitted and given a 12-day course of heparin therapy (200 mg. daily) without benefit.

Case 3. D. L., a 52-year-old retired male, entered the University of Michigan Dermatology Service on November 4, 1949, complaining of a chronic skin eruption. In 1942 he noticed the appearance of vesicles and bullae on his upper chest. These lesions were neither pruritic nor painful. Gradually, during a 2-month period, the bullae spread to involve the entire body. The patient was brought into the University Hospital at that time, seriously ill. He was treated with repeated transfusions and wet dressings, with some improvement. During the past 7 years his general condition has remained the same. He had received arsenic therapy and repeated courses of penicillin injections without improvement.

On examination the patient appeared to be in no acute distress. He had a generalized, exfoliative dermatitis. The skin felt infiltrated, and small nodules were palpated over the entire body.

Routine laboratory studies were not remarkable. The total serum proteins were 5.8 gm. per 100 ml., with 2.8 gm. albumin and 3.0 gm. globulin. The A/G ratio was 0.93. A skin biopsy was interpreted by the pathologist as being compatible with the diagnosis of pemphigus foliaceus.

At the time the patient was admitted, he was started on aureomycin 500 mg. 4 times daily. This was continued for 15 days along with application of 1% salicylic acid in yellow petrolatum to the entire skin. At the end of this time no improvement was seen. The aureomycin was discontinued and KPAB was begun on October 19, 1949. The dosage was gradually increased to 21 gm. per day. After 2 weeks there appeared to be noticeable improvement, characterized by diminished serous exudation and scaling. By November 22nd the improvement was such that the patient could be discharged to continue his KPAB at home.

He was unable to return until February 10, 1950; however, his supply of KPAB had

been exhausted by mid-December. Following this, there was an exacerbation of his eruption. KPAB was resumed and taken regularly. He returned on March 10, 1950, and was enthusiastic about his response. He had gained weight and clinical improvement was again evident. Unfortunately, economic factors prevented the patient from returning for further observation.

Case 4. C. P., a 50-year-old white female, was admitted to the University of Michigan Hospital on February 16, 1948, for treatment of a generalized bullous eruption which had appeared in mid-October, 1947. The diagnosis of pemphigus foliaceus was made, and she was placed on 18 gm. daily of KPAB for 10 days. However, the patient exhibited a severe psychosis which necessitated her transfer to another hospital. She gradually recovered from this episode and was readmitted on November 4, 1949. At this time the skin was more severely involved with innumerable bullae and vesicles, most of which were ruptured. There were many cracks and fissures. Nikolsky's sign was present. The mucous membranes were clear. The patient was very obese. Aside from the eruption, positive physical findings included generalized lymphadenopathy, and the liver was palpable 4 finger breadths below the costal margin.

Admission urinalysis and blood studies were normal.

Treatment consisted of KPAB (18 gm. daily), as well as potassium permanganate baths, gentian violet to denuded areas, and various antihistaminics for pruritus. This program was maintained from November, 1949, until June 20, 1950, when she was discharged from the hospital. Improvement had been minimal at best. She subsequently received several courses of cortisone therapy. These resulted in incomplete suppression of the disease process but were accompanied by the development of marked edema which necessitated interruption of therapy.

PEMPHIGUS ERYTHEMATODES. *Case 1.* G. B., a 68-year-old white male basket weaver, first visited the University of Michigan Dermatology Service on November 22, 1949, complaining of skin trouble of 4 months' duration. Before that time he had been in good health, with no skin disorders. At the onset he noted red, scaly, pruritic patches over both cheeks. These areas gradually increased in size so that the sides of the face, ears, behind the ears, and scalp were involved. Approximately 4 weeks before this visit he noted the onset of vesicles and bullae over the anterior chest, abdomen, arms, and axillae, which would arise on normal skin, open, drain, and then crust over. Those in the axillae had remained dry and papular. In spite of topical applications of a white ointment and a purple-red "paint" his lesions progressed.

Examination revealed a well-developed, rather well-nourished man who appeared chronically ill. Over the sides of the face, the ears, behind the ears, and in the scalp was an erythematous, greasy, scaled, symmetrical eruption which had somewhat the appearance of seborrheic dermatitis. There were dried circinate remains of bullae and vesicles over the anterior chest, upper arms, thighs and about the umbilicus. In the axillae there were vegetative lesions. All lesions were obscured by fuchsin applications.

The patient was advised to use a 1% salicylic acid in a washable base on the scaly lesions and to return in one week.

The patient returned on December 1st to be admitted. Examination at that time was the same as above. Nikolsky's phenomenon could be elicited on all normal appearing regions of the skin. The oral mucous membranes were clear. Two skin biopsies were obtained on December 2, 1949, and photographs were taken (Fig. 7*a*, *c*). The biopsies were read by the Department of Pathology as being compatible with a diagnosis of pemphigus.

Laboratory findings included the admission urinalysis which was within normal limits. The hemoglobin was 9.6 gm. and the leukocytes numbered 13,400 per c.mm. The total serum proteins were 7.6 gm. %, with 4.8 gm. albumin and 2.8 gm. globulin. The Kahn test on the blood serum was negative.

The diagnosis of pemphigus erythematodes was made and the patient was started on KPAB on December 2, 1949. He was receiving 18 gm. daily by December 7th. The drug was well tolerated and his skin began to clear soon after therapy was begun. By December 14th the face and scalp were almost entirely clear, and on December 24th the patient was discharged to continue the KPAB at home. He was instructed in the use of colloidal baths twice daily and was given a prescription of 1% salicylic acid in Mumford's base to apply to the face and body lesions. The trunk and back were the slowest to respond to treatment, with old, regressing lesions present in those areas at time of discharge.

The patient returned January 6, 1950, and was much improved. The Nikolsky sign was produced with difficulty. He continued on the same regimen and returned to the Dermatology Clinic January 25th, still improving and

without the appearance of new bullae. The patient's appearance on March 17th can be seen in Fig. 7*b*, and *d*. He remained on therapy, gained weight, and felt well when seen again on April 7, 1950. At that time the Nikolsky sign could not be elicited. Treatment was terminated, and he was instructed to return in the event of relapse.

Case 2. C. C., a 34-year-old colored housewife, was referred on August 2, 1951, from the Skin and Cancer Clinic of Philadelphia for a trial of KPAB therapy. She had pemphigus erythematodes which had progressed since its onset in September, 1948, despite therapy with ultra-violet light, sulfapyridine, oral and parenteral vitamin E, acetarsone, penicillin and terramycin.

Examination revealed a "butterfly" distribution of crusted, discoid plaques on the face. Follicular plugs were visible on the under surface of some of the crusts when the latter were removed. Purulent conjunctivitis was present. The scalp was covered by heavy, dry, grayish scales. Over the shoulders and upper parts of the arms were many denuded areas surrounded by narrow erythematous zones. In the presternal and interscapular areas were noted heaped up crusted lesions with a purulent, malodorous discharge seeping from their edges. Discrete, flaccid, intact bullae, up to 3 cm. in diameter, were present in many areas of otherwise apparently normal skin. Nikolsky's sign was easily elicited.

Routine blood studies revealed a slight normocytic, normochromic anemia, but the leukocyte values were within normal limits, as were the urinalysis results.

The patient was begun on KPAB, 30 ml. of the 10% solution, every 3 hours for 7 doses daily. There was an initial flare of lesions during the first few days of treatment, followed by slight improvement over the succeeding weeks. Improvement was characterized by diminished incidence of bullous formation, as well as decreased size of lesions. Weeping from the denuded areas decreased noticeably. Nikolsky's sign, however, was still readily produced. During the next 8 months, the patient took 21 to 24 gm. daily of either KPAB or NaPAB. The cutaneous process was at no time completely suppressed, although there were periods of greater improvement during cold weather, and exacerbations during warm weather. In view of the failure to achieve control of the process with KPAB alone, it was planned to add cortisone to the treatment program. Because of economic factors, however, adequate therapy was not feasible on an outpatient basis, and the patient entered a Veterans Administration Hospital, in June, 1952. There, considerably more improvement of the bullous component was achieved with ACTH and cortisone, but the disorder was not completely suppressed even with high dosage hormonal therapy.

Case 3. J.G., a 32-year-old white male, had been in good health until July, 1954, when he became sunburned while deep sea fishing. He noted a small blister on the skin of the right lower jaw. This broke spontaneously and gradually enlarged. About a month later, additional lesions appeared on the anterior chest surface and the lower left jaw. All of these lesions began as papules, developed blebs, and then ruptured, leaving open sores which continued to enlarge.

In September, oral and conjunctival lesions were first noted. At that time, he was admitted to the St. Francis Hospital in Trenton, N. J., where the diagnosis of pemphigus erythematodes was made. During the course of study there, a large, sharply demarcated tumor mass was detected in the anterior portion of the upper lobe of the left lung. There was observed paradoxical movement of the left hemidiaphragm. There were no clinical signs or symptoms attributable to the intrathoracic tumor.

Because of the persistence of skin lesions, the patient was referred to Dr. Carroll S. Wright for treatment. He received hydrocortisone, 20 mg. every 8 hours, and some ACTH, without improvement.

Chloroquine diphosphate, 250 mg. q.i.d., was then tried without benefit. A positive Nikolsky sign was now readily elicited, and pemphigus erythematodes was diagnosed. He was referred for KPAB therapy on January 26, 1955. Examination revealed erythematous denuded, weeping areas, irregular in size and outline on the lower jaw, the neck, chest, axillae, (Fig. 8*a*), penis, scrotum, and inguinal regions, the buttocks and thighs. In addition, there was extensive ulceration of the oral mucosa. Conjunctivitis was marked. Hoarseness was present. He was placed on hydrocortisone, 20 mg. every 8 hours, and 30 ml. of KPAB, 6 times daily. Outpatient management continued for 3 weeks, with considerable improvement of the skin lesions. The axillary areas had healed sufficiently to permit him to raise his arms above his head without discomfort. Roentgen-ray examination of the chest on February 14, 1955, revealed a large mass projecting to the left from the upper anterior mediastinum, and a smaller mass projecting from the right side of the mediastinum (Fig. 8*c*, *d*). Paradoxical movement of the

left leaf of the diaphragm was noted fluoroscopically.

Because of increased hoarseness, cough and chest pain, the patient was admitted to the Temple University Hospital on February 23rd for palliative therapy of the intrathoracic lesion. Needle biopsy of the mediastinal mass was performed, and the pathologic diagnosis of adenocarcinoma was made. The lesion failed to respond, first to a course of nitrogen mustard therapy (24 mg. total), and secondly, to Roentgen-ray irradiation. His clinical condition progressively deteriorated, and he expired suddenly on April 14, 1955. During the course of attempted palliative therapy for the neoplasm, however, the treatment regimen of hydrocortisone and KPAB was maintained at the same dosage level as at the beginning of treatment. Photographs taken after 2 months of therapy show the improvement which had been achieved in the cutaneous lesions during that period (Fig. 8*b*).

OCULAR PEMPHIGUS. *Case 1.* M. W., a 62-year-old white female, was referred on December 19, 1949, by Dr. F. Bruce Fralick and Dr. Fleming A. Barbour for treatment of ocular pemphigus. The patient had had bullous lesions of the oral and nasal mucous membranes for approximately 10 years. Intermittent conjunctival involvement had been present for several years, but had been persistently troublesome during the past year. There had been no cutaneous manifestations at any time.

After base-line studies had been completed, the patient was started on 18 gm. daily of KPAB on December 20, 1949. Two weeks later, the ocular conjunctivae appeared less inflamed, and she stated she could see better. Buccal involvement was still evident, but there was diminished pain. The dosage of KPAB was reduced to 15 gm. daily over the next 6 weeks. On January 27, 1950, the patient was examined again by Dr. Fralick. "The patient states that she can now thread her own needle for the first time in over a year. Vision is same in the right eye (6/12 with correction) and slightly better in the left eye (6/9 with correction). The eyes were now moist and the corneas clear." The patient's mouth was also more comfortable, with increased moisture and less pain. KPAB was continued for 3 more weeks, but the patient failed to return for further treatment. Through correspondence with Dr. Fleming A. Barbour, however, it was learned that the patient had subsequently remained quite comfortable. On December 7, 1951, he found her corrected vision to be 20/25 O.D. and 20/50 O.S. Her nose and throat, however, had not shown further improvement.

Results. The over-all results of KPAB therapy in the 18 patients with various forms of pemphigus are summarized in Table 1. The clinical response was classified as "excellent" if complete suppression of the cutaneous manifestations was achieved. Seven cases of pemphigus vulgaris and one with pemphigus erythematodes had excellent results. Patients with marked though incomplete control of the disease process constitute the "good" response group, while lesser improvement was considered to be only a "fair" result. There were 5 cases in the former category and 2 patients in the latter. Although 3 patients failed to improve, 2 of these were treated only briefly, which in the light of subsequent experience was of too short duration to permit an adequate therapeutic trial of the drug.

Discussion. The preceding histories and illustrations clearly indicate the character and degree of improvement in pemphigus cases treated with potassium para-aminobenzoate, alone or in combination with steroid hormones. The largest experience was with cases of pemphigus vulgaris. In this group improvement was gradual and was characterized by cessation of exudation, subsidence of blister formation, followed by epithelialization and hyperpigmentation. The latter faded during sustained remissions, as, for example, in Case 9 (Fig. 4*a-d*). Weight gain and improvement in hemoglobin values were noted in a number of patients. Plasma specimens from two of these cases were subjected to electrophoretic analysis[1]. General improvement in the protein pattern was detected during the period of KPAB treatment[1].

Duration of therapy varied from a few weeks to more than 2 years. In several patients whose disease was

completely suppressed, the KPAB was discontinued and they were observed for relapse. Two have remained in remission for more than 2 years. Others have relapsed and have expired while under treatment elsewhere with different regimens, usually cortisone.

Pemphigus foliaceus responded incompletely to KPAB therapy, although 2 of the 4 cases exhibited marked improvement. It is of interest that both of these subjects were later treated with cortisone alone without added improvement.

TABLE 1.—RESULTS OF KPAB THERAPY IN 18 CASES OF PEMPHIGUS

		Clinical Response			
Type of Pemphigus	*No. of Cases*	*None*	*Fair*	*Good*	*Excellent*
P. vulgaris	10	2°		1	7‡
P. foliaceus	4	1	1°°	2	
P. erythematodes	3		1	1°°†	1
Ocular pemphigus	1			1°°	
Total	18	3	2	5	8

°Treated for less than 3 weeks.
°°Treatment interrupted, possibly before maximal result achieved.
†Combined KPAB-cortisone therapy; patient died of malignancy.
‡Two of these patients also received cortisone.

The patients with pemphigus erythematosus, although few in number, showed a wide range of response to KPAB treatment, while the single patient with ocular pemphigus experienced definite improvement in the ocular manifestations of her disease.

Two patients with pemphigus vulgaris and one with pemphigus erythematosus were given combined KPAB and cortisone therapy. All 3 had previously had steroid therapy without sustained control of the disease process. The combination program resulted in complete suppression in both cases of pemphigus vulgaris (Cases 9 and 10). The third patient was improving with respect to his pemphigus erythematosus but died of adenocarcinomatosis while under treatment. It is of interest that the cutaneous improvement in these patients was achieved with considerably lower doses of cortisone than had been previously used alone. Thus, the possibility of a synergistic effect between KPAB and cortisone is suggested. In this connection may be mentioned the report of Bonner and his associates[2]. These workers determined the cortisone requirements of a patient with pemphigus and then reduced the dosage to a sub-effective level. When potassium para-aminobenzoate was added to the treatment program, healing of the skin lesions followed. The same observers also obtained evidence of KPAB-cortisone synergism in rheumatoid arthritis, confirming the findings of Wiesel *et al.*[13,14], and Zarafonetis *et al.*[22].

In addition to these published reports, Wiener[12] describes a patient with pemphigus erythematosus who required 750 mg. of cortisone daily to control her skin manifestations. On this program, however, severe mental depression resulted, and the patient was admitted to a psychiatric service for electroshock therapy. At the same time she was given Potaba, 18 gm. daily. The patient gradually improved and the dosage of cortisone was slowly re-

duced to a maintenance level of 150 mg. daily. On several occasions, attempts to reduce the dosage of either drug resulted in a prompt exacerbation of the skin disorder.

The use of KPAB supplies para-aminobenzoate for the treatment of pemphigus and also an adequate potassium supplement for cortisone therapy when the two are combined.

The optimal KPAB dosage for the treatment of pemphigus is 18 gm. or more daily, in divided doses. The therapeutic regimen is continued for months or years. In rapidly progressive pemphigus, KPAB may only retard the disease. However, when the process is moderately active, KPAB therapy may give rise to striking improvement which can be sustained, apparently indefinitely.

Untoward reactions to KPAB have been previously documented[16-23]. These consist mainly of gastrointestinal complaints such as anorexia and nausea, which are, however, much less frequently encountered with KPAB than with other para-aminobenzoic acid preparations. Anorexia and nausea will usually subside upon omission of the drug for a day or so, and treatment may be resumed as soon as the patient is eating well. By omission of the drug during periods of poor dietary intake, it is also possible to prevent the occurrence of hypoglycemia such as appeared in Case 2 of the pemphigus vulgaris group. The basis for hypoglycemia is not known, but it seems that KPAB somehow interferes with glyconeogenesis.

Case 2 illustrates another important point, namely, that sulfonamide drugs should not be administered concomittantly with PABA compounds. These substances are mutually antagonistic, each preventing the effect desired of the other.

The above effects of KPAB cannot be termed toxic reactions in a true sense. Indeed, KPAB is remarkably free of straight toxic reactions. For example, rats[4,10] and guinea-pigs[4] have been given large doses (2 to 4.5 gm./kg.) of para-aminobenzoic acid for 2 to 6 months without producing detectable histologic changes. Cruickshank and Mitchell[4] did observe varying degrees of fatty change in the heart, liver, and kidneys in 6 of 9 rabbits. These animals, however, weighed 1.85 to 3.9 kg. and received up to 11 gm. per day of para-aminobenzoic acid. Calculated at an average of 5.0 gm. per kg. of body weight, and translated in terms of clinical usage, this would be equivalent to 350 gm. a day for a 70 kg. man. This amount is 15 to 20 times the amount of KPAB given to the pemphigus cases described herein. It is of further interest that insofar as the production of fatty change was concerned, Cruickshank and Mitchell found that when the solution of para-aminobenzoic acid in sodium bicarbonate was permitted to stand after preparation, no fatty changes were induced. These results suggest that fully neutralized preparations of para-aminobenzoic acid are nontoxic. This is not to say, however, that KPAB does not give rise to reactions of hypersensitivity. Indeed, instances of drug fever and drug rash have been observed. In retrospect, it appears that the instance of "toxic hepatitis" reported by us[19] was another example of an hypersensitivity reaction. Leukopenia has been observed but its significance is difficult to assess since there is often return to normal values despite continued administration of the drug. In more than 500 patients treated in this and related studies no agranulocytosis has been encountered. Furthermore, it should be noted that the prolonged use of large doses of KPAB is free of such hazards as perforation of peptic ulcer, toxic psychosis, hyperten-

sion, protein catabolism, osteoporosis, and so forth which stalk patients receiving steroid therapy for comparable periods of time[6,9].

The mechanism by which KPAB mediates its effects in pemphigus is not known. It must act at a fundamental metabolic level in order to modify the manifestations of pemphigus, scleroderma, dermatomyositis, and a variety of other disorders. Much is known, of course, about many biochemical actions of para-aminobenzoic acid[3,15]. As yet, however, it has not been possible to relate this information to the clinical states under consideration. Workers in the past have considered para-aminobenzoic acid to be a member of the B-complex group of vitamins. More recently, Briggs and Daft[3] have suggested that this substance should no longer be regarded as a vitamin but rather as a microbial nutrilite. There is no evidence today that the compound is required for any higher animal. Whatever the ultimate decision regarding this question, however, it should be evident that the massive doses of KPAB which have been administered to patients in this and other clinical studies represent a pharmacologic use of the compound.

Summary and Conclusions. 1. Potassium para-aminobenzoate was administered in 18 to 24 gm. total daily doses to 18 patients with various forms of pemphigus.

2. All 8 patients with pemphigus vulgaris who received KPAB therapy for more than a month responded with marked to complete suppression of the disorder.

3. Pemphigus foliaceus responded incompletely, although 2 of 4 cases exhibited good clinical improvement.

4. One patient with pemphigus erythematodes cleared completely, another had an intermediate response, while a third was only slightly improved.

5. Definite benefit was experienced by the only patient of this group with ocular pemphigus.

6. Gratifying results were obtained in 3 patients who were treated with both KPAB and cortisone, after large doses of steroid therapy alone had failed to control their disease satisfactorily.

7. The only potentially serious complication of KPAB therapy is hypoglycemia. This may be avoided by interrupting therapy if the patient fails to eat for any reason at all. The drug may be resumed as soon as the patient is again eating normally.

8. Potassium para-aminobenzoate, properly administered, alone or in combination with steroid hormones, appears to offer a valuable adjunct to the management of several forms of pemphigus.

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SUMMARIO E CONCLUSIONES IN INTERLINGUA

Tractamento de Pemphigus con Para-Aminobenzoato de Kalium

1. Para-aminobenzoato de kalium esseva administrate in dosages total de 18 a 24 g per die a 18 patientes con varie formas de pemphigus.

2. Le 8 patientes con pemphigus vulgar qui recipeva le therapia a para-aminobenzoato de kalium durante plus que un mense respondeva con un marcate o complete suppression del disordine.

3. Pemphigus foliacee respondeva incompletemente, ben que 2 del 4 casos exhibiva un bon grado de melioration clinic.

4. Un patiente con pemphigus erythematose monstrava un complete suppression del disordine; un secunde habeva un responsa intermediari; e un tertie esseva solo levemente meliorate.

5. Un melioration definite esseva experientiate per le sol patiente de iste gruppo qui habeva pemphigus ocular.

6. Resultatos incoragiante esseva obtenite in 3 patientes qui esseva tractate con para-aminobenzoato de kalium e cortisona post que un therapia a large doses de steroides sol non habeva succedite a subjugar lor morbo satisfactorimente.

7. Le sol potentialmente serie complication del therapia a para-aminobenzoato de kalium es hypoglycemia. Isto pote evitar se per un interruption del therapia quando le patiente refusa mangiar pro un ration o un altere. Le medication pote esser recomenciate si tosto que le patiente mangia de novo normalmente.

8. Para-aminobenzoato de kalium, correctemente administrate, sol o in combination con hormones steroide, pare representar un importante adjuncto in le tractamento de varie formas de pemphigus.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

(See page 26 for original article)

Evalutation Clinic del Diuretico Mersoben

1. Un serie de 85 patientes recipeva injectiones unic de Mersoben pro probar su activitate diuretic.

2. Mersoben es un potente diuretico. Illo ha le avantage de contenir un relativemente basse quantitate de mercurio.

3. Con le doses describite, effectos lateral de Mersoben es minimal. Nos ha notate nulle evidentia de mal effectos local, renal, o systemic, excepte le occurrentia de infrequente dolores local e rar reactiones de sensibilitate.

THEOPHYLLINE CONCENTRATION IN BLOOD PLASMA FOLLOWING RECTAL ADMINISTRATION OF AMINOPHYLLINE*

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The following investigation was undertaken to determine the efficiency of intrarectal administration of aminophylline, and the best suitable suppository bases for this purpose.

The concentration of theophylline in blood plasma is the most reliable indicator of the rate of absorption of this drug. Therefore, we determined theophylline levels in plasma of 30 patients following the administration of aminophylline rectally in the form of suppositories and intravenously. We used for these determinations the ultraviolet spectrophotometric method[3] of Schack and Waxler.

Method and Materials. The Schack-Waxler method consists briefly of repeated extraction of 3 ml. of plasma with a chloroform-isopropyl alcohol mixture and subsequent re-extraction of the filtrate of the first extraction with 0.1 NaOH. The absorption coefficient of the alkaline extract is then determined as measured at wave length 277 mu. in the quartz cuvette of the Beckman Model DU Quartz Spectrophotometer provided with ultraviolet accessories.

Specific precautions were found to be important. These include the use of small original bottles of isopropyl alcohol which were opened anew each time the determinations were performed, use of an electrically driven shaker to speed the extraction, and careful pipetting of the aqueous layer from the separation funnel.

The Schack-Waxler method was very satisfactory in our hands and we obtained an absorption curve of theophylline almost identical with that reported by Schack and Waxler with a maximum of absorption at 275 to 277 mu.

There was also a perfect linear relationship between the concentration of theophylline in the alkaline solution and the optical density as read at 277 mu. (Fig. 1). In our determinations, the optical density at 277 mu. wave length for a theophylline solution containing 10 μg. per ml. 0.1 N NaOH was 0.542, or 4.7% lower than the reading of 0.569 reported by Schack and Waxler. This insignificant difference was the result of our absorption peak being at 275 rather than 277 mu. wave length. In order to have data comparable to those of Schack and Waxler,

*Supported in part by the Research Grant-in-aid from G. D. Searle & Company, Chicago, Illinois.

however, we performed all of our readings at 277 mu. wave length and calculated accordingly.

Recovery tests performed on three different samples of normal human plasma to which were added varying concentrations of theophylline are listed in Table 1. The data obtained indicate a very satisfactory recovery of the theophylline, from 84.8 to 93.0% with an average of 88%. The concentration of theophylline was 1.0 to 16.0 μg. per ml. of plasma, which corresponds to that observed in our actual studies. The recovery of theophylline from the plasma at a concentration of 20.0 μg./ml. was still better, 94.1%. Although our recovery figures are somewhat below those reported by Schack and Waxler[3] (96.0 to 110.0% at a range of 1.25 to 10.0 μg./ml.), we consider the method to be very accurate. This opinion was further verified by a good duplication of results.

Since caffeine and barbiturates interfere with the readings of theophylline absorption[3], the patients were advised not to have coffee,

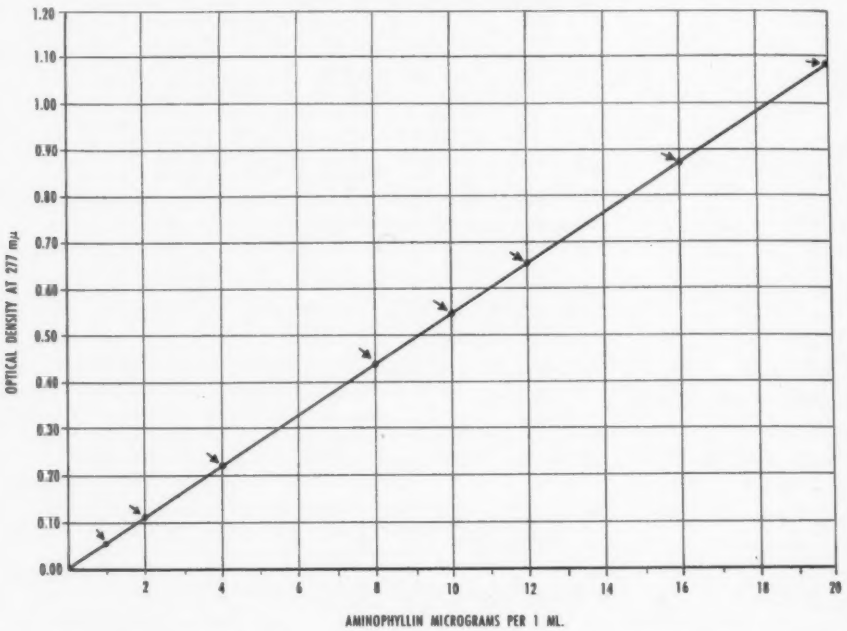

Fig. 1.—Spectrophotometric readings at 277 mu wave lengths of aminophylline standards at various concentrations.

TABLE 1.—RECOVERY OF AMINOPHYLLINE ADDED TO HUMAN PLASMA (*IN VITRO*)

Aminophylline μg./ml.				*Recovery %*	
	Recovered				
Added	*In Plasma A*	*In Plasma B*	*In Plasma C*	*Uncorrected*	*Corrected According to the Standard Reading**
1.0	..	0.63	1.01	81.5	85.1
2.0	2.06	1.18	..	81.0	84.8
4.0	..	3.23	3.40	83.0	86.9
8.0	6.38	7.31	7.60	88.8	93.0
12.0	9.79	10.79	10.80	87.2	91.3
16.0	12.35	14.36	12.94	82.6	86.5
20.0	18.10	18.52	19.87	94.1	98.5

* Correction of + 4.7% was applied to the uncorrected calculations.

TABLE 2.—PLASMA LEVELS OF THEOPHYLLINE FOLLOWING RECTAL ADMINISTRATION OF 0.5 GM. AMINOPHYLLINE IN FORM OF SUPPOSITORY

Suppository Number and Composition	*Case Number Initials, Sex, Age*	*Theophylline in Plasma in μg./100 ml. Hours after Administration* 1	2	3	4	6	8
1—Carbowax base	1—A.B., m., 60	..	424	..	407	466	..
	2—J.S., m., 32	..	168	..	441	399	..
	3—A.O., f., 43	..	748	..	1018	1005	..
2—Polyethylene-glycol base	4—R.O., m., 43	..	177	..	118	252	..
	5—C.R., m., 32	..	0*	..	80	50	..
	6—E.O., f., 46	..	168	..	424	910	..
	7—A.S., m., 60	..	252	..	269	361	..
3—Mannitol base	8—R.R., m., 22	..	124	..	609	634	..
	9—R.B., m., 47	..	177	..	164	151	..
	10—J.G., m., 60	97	294	..	769	740	..
4—Buffered carbowax base	11—G.L., m., 25	..	366	372	..	..	..
	12—M.E., m., 42	..	895	1050	1325	..	..
	13—F.E., f., 39	..	694	940	1026**	..	..
	14—M.E., m., 28	..	470	..	298	118	..
	15—T.C., f., 54	..	693	..	723	644	..
	16—G.L., m., 60	..	925	..	756	1512	..
5—Placebo	17—C.P., f., 13	..	0	..	0	0	..
	18—J.R., f., 30	0	17	..	21	..	..
	19—W.P., m., 19	..	0	..	0	0	..
	20—G.R., m., 46	..	4	..	0	0	..
6—With 0.1 gm. pentobarbital sodium and 0.065 gm. benzocaine in mannitol base	21—H.C., f., 66	744†	..	..	1430†	..	..
	22—E.C., f., 65	..	42***	..	25	0	..
7—With 0.06 gm. benzocaine in mannitol base	23—A.H., m., 24	151	449	..	764	..	..
	24—C.I., m., 23	113	344	..	542	..	..
	25—M.M., f., 65	..	46	..	408	382	..
	26—H.L., f., 56	..	840	..	824	1095	..
	27—P.R., m., 25	461	..	536	..	745	827
	28—A.B., f., 69	..	..	126	..	655	1014
	29—C.R., f., 60	..	..	662	..	366	164

* Suppository partly expelled after one and three-quarter hours.
** Suppository partly expelled after four hours.
*** Suppository expelled shortly after insertion.
† High levels in plasma could be due to the absorption of pentobarbital into the blood from the suppository.

TABLE 3.—AVERAGED PLASMA LEVELS OF THEOPHYLLINE FOLLOWING RECTAL AND INTRAVENOUS ADMINISTRATION OF 0.5 GM. AMINOPHYLLINE

Route of Administration	*Aminophylline in Plasma in μg./100 ml. (means with standard deviation) Hours after Administration* 1	2	3	4	6	8
Suppository # 1*	..	447 ± 237	..	622 ± 281	623 ± 270	..
Suppository # 2	..	149 ± 92	..	233 ± 134	393 ± 318	..
Suppository # 3	..	198 ± 71	..	514 ± 165	508 ± 258	..
Suppository # 4	..	674 ± 203	789 ± 298	826 ± 342	758 ± 571	..
Suppository # 7	242 ± 156	420 ± 283	441 ± 227	635 ± 169	649 ± 270	668 ± 364
Intravenously (in 20 ml. water)	1462 ± 175	..	1402 ± 290	..	..	..
Placebo suppository	..	5 ± 7	..	5 ± 9	0 ± 0	..

* Suppository # 1: Carbowax base.
Suppository #2: Polyethylene-glycol base.
Suppository # 3: Mannitol base.
Suppository # 4: Buffered carbowax base.
Suppository # 7: With 0.06 gm. benzocaine, in mannitol base.

tea or barbiturates for at least 24 hours before the examination. Moreover, immediately before each test was started a fasting blood specimen was withdrawn and used as a blank reading. This was processed in the same way as the other blood samples, and the absorption noted at 277 mu. was deducted from the readings of each of the blood samples collected after administration of theophylline. Thus, the absorption increments obtained during each test were due only to theophylline. This procedure was necessary because various blank readings showed variations in spite of being collected under similar fasting conditions and with the use of the same anticoagulants (sodium, potassium and lithium oxalate mixture at a constant concentration). The range of 30 different blank absorption readings was an optical density of 0.095 to 0.306, with a mean reading of 0.146, a standard deviation of 0.044, and a coefficient of variation of 30.1%. Our blank values were therefore approximately twice as high as those encountered by Schack and Waxler who reported an averaged optical density of 0.07, with a standard deviation of 0.02.

The reliability of the method was checked by control tests with the use of placebo suppositories, as well as by blood analyses without administration of medication; the person performing the blood analyses was not aware of these facts. Tables 2 and 3 show that the readings obtained on these blood samples equaled zero if the limitations of the accuracy of the method at low concentration[3] are taken into consideration.

Studies were performed on 30 patients, 17 male and 13 female patients, of whom two were less than 20 years of age, ten were between 20 and 39, eight between 40 and 59, nine between 60 and 69, and one patient over 83 years of age. Fifteen patients, or one-half of the total, were convalescing after small operative procedures; 6 had congestive cardiovascular disease, 3 had liver disease, and 6 patients had various other diseases, such as brain tumor, uterine fibroids, carcinoma of the breast, or peptic ulcer.

In 26 of these patients various aminophylline suppositories were used and in 4 patients placebo tests were performed. The blood samples were collected under fasting conditions immediately before insertion of the suppository as well as at various intervals from one to 8 hours thereafter. Four to five blood collections were obtained from each patient during the 3 to 8 hours of the testing period.

Seven different types of suppositories were used, of which one (V) was a placebo with a mannitol base, four others (I to IV and VII) contained 0.5 gm. of aminophylline in various media, and one (VI) contained 0.5 gm. of aminophylline together with 0.1 gm. of pentobarbital sodium and 0.06 gm. of benzocaine*. Information on the composition of these suppositories was withheld from persons performing the assays to ascertain impartiality of observation. In two individuals 0.5 gm. of aminophylline dissolved in 20 ml. of water was injected intravenously and the blood was collected at intervals of 10 minutes during the first hour and two and three hours thereafter.

Results. BLOOD PLASMA LEVELS OF THEOPHYLLINE FOLLOWING ADMINISTRATION OF AMINOPHYLLINE SUPPOSITORIES. The data obtained are listed in Tables 2 to 4 and in Figs. 3 to 5. It is apparent from these data that highly significant and sustained blood plasma levels of theophylline were obtained with some of the preparations used, although the rate of rectal absorption of theophylline from various types of suppositories differed markedly, and wide individual variations were observed with the same type of suppository in various subjects. Blood plasma levels of theophylline ranged from 46 to 1,510 μg./100 ml. Four to 6 hours after insertion of the suppository, the levels exceeded 250 μg./100 ml. in 39, or approximately 80% of 49 blood samples; in 13 samples the levels ranged from 250 to 500 μg./100 ml.; in 17 samples from 500 to 1,000 μg./100 ml.; and in 9 samples from 1,000 to 1,512 μg./100 ml.

The following results were obtained with various types of suppositories containing 0.5 gm. of aminophylline:

Suppository I, carbowax base (currently available): Blood levels were determined in 3 patients. Results indicate that very satisfactory blood plasma levels were obtained (Table 2). These levels were between 400 and 1,000 μg., averaging 600 μg., per 100 ml., between

*Generously supplied by G. D. Searle & Company, Chicago, Illinois.

the fourth and sixth hour after insertion of the suppository.

Suppository II, polyethylene-glycol base (currently available): Blood assays were performed on 4 patients. Even when the suppository was well retained, which was not always the case with this preparation, theophylline levels were much lower than those observed with the previous preparation (Table 2). Blood plasma levels 4 to 6 hours after administration were between 118 and 910 μg./100 ml., and approximately one-half of the average level obtained with suppository I.

Suppository III, mannitol base (experimental): Plasma levels of theophylline were obtained in 3 patients. The values were on the average somewhat lower than those observed with suppository I, particularly 2 hours after administration, but much higher than those obtained with suppository II (Table 2, Fig. 2).

TABLE 4.—COEFFICIENT OF VARIATIONS IN PER CENT OF PLASMA LEVELS OF THEOPHYLLINE FOLLOWING RECTAL ADMINISTRATION OF 0.5 GM. AMINOPHYLLINE IN FORM OF SUPPOSITORY.

Suppository Number	*Hours after Administration*					
	1	*2*	*3*	*4*	*6*	*8*
1*	..	53.0	..	45.2	43.3	..
2	..	61.7	..	60.1	89.0	..
3	..	35.9	..	31.7	50.8	..
4	..	30.1	37.8	41.4	75.3	..
7	64.4	67.4	51.5	26.6	41.6	54.5

* As in Table 3.

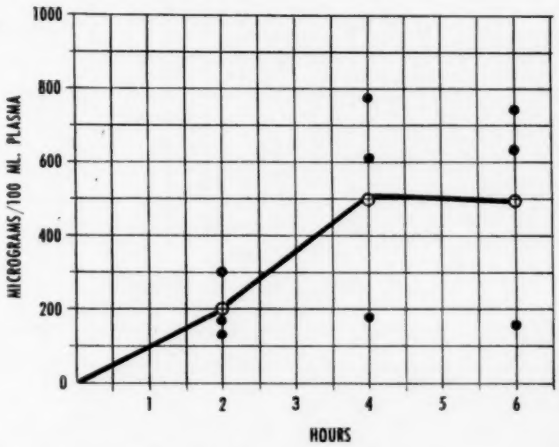

Fig. 2.—Suppository No. 3.

Suppository IV, buffered carbowax base (currently available): This suppository was tested in six patients (Table 2, Fig. 3). Very high average blood plasma levels were observed and action appeared to be very well sustained throughout the second to sixth hour of the experimental period with a peak at the fourth hour. Of 17 blood specimens collected between the sec-

ond and the sixth hour, 15, or approximately 90%, showed levels above 365 μg./100 ml.; in 7 subjects the levels were between 500 and 1,000 μg./100 ml., and in 3 subjects (four blood samples) an excessively high concentration of theophylline in plasma, ranging from 1,026 to 1,512 μg./100 ml., was

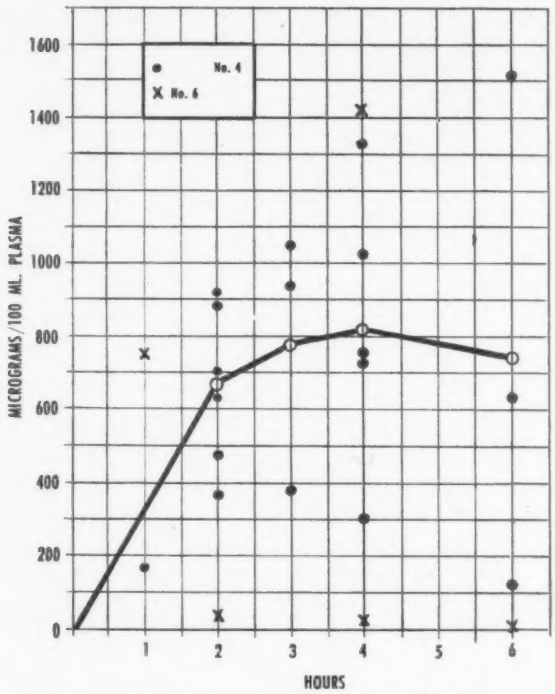

Fig. 3.—Suppository Nos. 4 and 6.

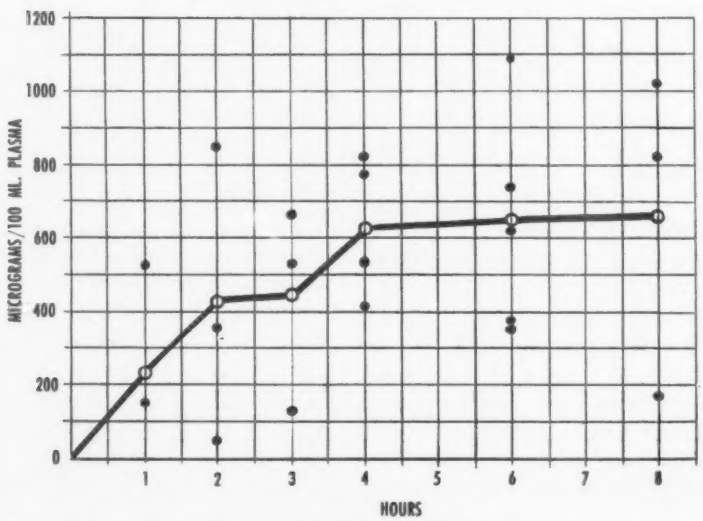

Fig. 4.—Suppository No. 7

obtained. Although the apparent rate of disintegration of the suppository in the rectum was rather slow (from one and one-half to two hours)[1], the blood levels at the end of the second hour were high (366 to 925 μg./100 ml.) so that the average theophylline concentration at this time was 647 μg./100 ml.; a much higher level than that obtained with other suppositories.

Suppository VI, fatty alcohol base, with 0.1 gm. of pentobarbital sodium and 0.06 gm. of benzocaine (currently available): Tests were performed on 2 patients (Table 2, Fig. 3). In one of these no plasma levels of theophylline were obtained, apparently the result of early expelling of the suppository from the rectum. In the second patient an excessively high optical density reading was obtained, which probably was caused by interference of the pentobarbital contained in the suppository. No inferences could be made regarding the absorption of the theophylline contained in this product.

Suppository VII, mannitol base with .06 gm. of benzocaine (experimental): Tests were performed on 7 patients. The data were obtained to cover almost every hour for eight hours after administration of the suppository (Table 2, Fig. 4). Blood levels obtained were similar to those obtained with suppository I. The range of values obtained during the second and third hour was from 344 to 849 μg./100 ml. in five of seven blood samples, with an average of approximately 420 to 440 μg./100 ml. Levels ranged from 366 to 1,095 μg./100 ml. in 11 of 12 blood specimens tested during the fourth to eighth hour. The average plasma level of theophylline was approximately 650 μg./100 ml. through the fourth, sixth and eighth hours of

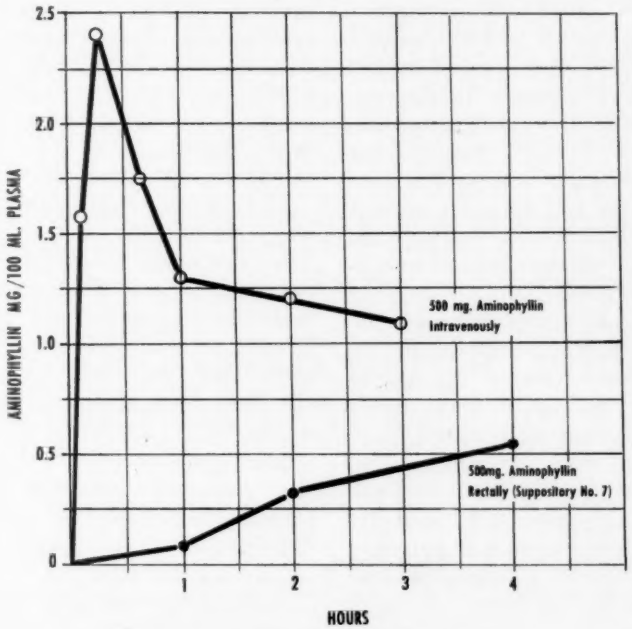

Fig. 5.—Case 24. C.T.M., 23 years.

the test period, indicative of a well-sustained action.

Comment. The summary of results, with the means, standard deviations and coefficients of variation of all tests performed, is tabulated in Tables 3 and 4.

It appears from these data that it is possible to obtain good absorption of theophylline into the blood from the rectum. This is shown by fairly high theophylline levels two hours after insertion of the aminophylline suppository (suppositories IV and VII) and a further increase with a peak between the fourth and sixth hour with all preparations studied. This pattern of absorption is in accordance with earlier observations of other authors[2,5].

Depending on the type of suppository used, differences in the patterns of absorption of theophylline were observed. Suppositories I and III resulted in highest plasma levels between the fourth and sixth hour; suppository IV caused high levels between the second and sixth hour; and peak levels between the fourth and eighth hour were observed with suppository VII.

The range of theophylline levels obtained with suppositories II and III was similar to that reported by other investigators[2,6], that is, from 200 to 300 μg./100 ml. The levels obtained with suppositories I, IV and VII were, however, definitely higher than those reported earlier[2-4], although some of them fall in the range reported by Waxler and Schack[5]. These high levels may be attributed to good disintegration of the base used in these new-type suppositories and to good intrarectal retention.

Mean plasma levels of theophylline 2 to 6 hours after insertion of aminophylline suppositories in a carbowax base (I) and a mannitol base with benzocaine (VII) were almost identical (Tables 3 and 4). It should be repeated that the average plasma levels of theophylline following the administration of suppository VII were higher than those observed following suppositories with a mannitol base without the addition of benzocaine (III) and certainly much higher than those recorded after the use of suppositories containing a polyethylene-glycol base (II). The average plasma levels of theophylline 2 to 6 hours after the administration of suppository IV were higher than those obtained with suppository VII. However, because of large standard deviations observed and the small number of observations performed, this difference is not statistically significant, the "p" value being at any time much above 0.1.

The maintenance of plasma levels was best with the use of suppository VII, containing a mannitol base with benzocaine, and the average curve drawn in Fig. 4 shows a plateau 4 to 8 hours after insertion of the suppository. The uniformity of results was also best with this preparation, as is shown by the lowest coefficient of variations, 26.6 and 41.6% at the fourth and sixth hour after administration of the drug, as compared with greater variability of levels observed with other preparations.

A blood level of theophylline of approximately 500 μg./100 ml. is necessary for a diuretic effect[4]; with aminophylline suppositories III, IV and VII this level was almost uniformly obtained. This threshhold of diuretic action was exceeded in 8 of the 10 subjects receiving suppositories containing a mannitol base, with or without benzocaine, (suppositories III and VII) and in 4 of the 6 subjects receiving suppository IV with a buffered carbowax base.

BLOOD PLASMA LEVELS OF THEOPHYLLINE FOLLOWING INTRAVENOUS ADMINISTRATION OF AMINOPHYLLINE. In 2 sub-

jects plasma levels of theophylline were determined (Table 5) following the intravenous administration of 0.5 gm. of aminophylline dissolved in 20 ml. of water. Within the first 10 to 20 minutes after injection very high plasma levels were obtained, exceeding 2,000 μg./100 ml. Shortly thereafter the theophylline concentration in plasma decreased rapidly so that one hour after injection one-half to three-fourths of the initial peak levels was observed. In view of data listed in the literature[2,5] which indicate very fast decrease in theophylline levels after intravenous administration, the levels at the end of the first hour in our 2 subjects were surprisingly well maintained throughout the entire 3-hour period of observation following injection.

TABLE 5.—PLASMA LEVELS OF THEOPHYLLINE FOLLOWING INTRAVENOUS ADMINISTRATION OF 0.5 GM. AMINOPHYLLINE IN 20 ML. WATER

Time after Intravenous Injection	*Plasma Levels of Theophylline in μg./100 ml.*	
	Case 24, C. T., m., 23	*Case 30, C. Z., f., 83*
10 minutes	1632	2023
20 minutes	2445	1982
30 minutes	..	2167
40 minutes	1747	..
1 hour	1291	1638
2 hours	1203	..
3 hours	1110	1693

It should be noted also that plasma concentrations observed in these 2 subjects were more than three times higher than the figures of 600 to 700 μg./100 ml. reported in the literature[2,5]. This discrepancy is due in part to the larger dose injected in our tests (0.5 gm. as compared to the dose of 0.25 to 0.30 gm. used by Waxler and Schack[5] and Broadwall[2]); variance also resulted from the timing of blood collection which in our study was started as early as 10 minutes after injection, compared to a 15 to 30-minute time lapse observed by other authors[2,5].

The comparison of blood plasma levels of theophylline after intravenous (Table 5) and rectal (Fig. 3) administration of aminophylline shows that peak levels are much higher and are obtained much more rapidly after intravenous administration of aminophylline than after rectal administration in the form of suppositories. This is well illustrated by Patient 24 to whom we administered 500 mg. of aminophylline both intravenously and rectally (Fig. 5). The differences in the plasma levels following intravenous and rectal administration are obvious.

Summary. Aminophylline was administered rectally in the form of suppositories to 30 subjects and plasma levels of theophylline were determined for a period of 1 to 8 hours. The Schack-Waxler[3] ultraviolet spectrophotometric method was used for this purpose and was found to be very satisfactory. In each patient plasma levels obtained after administration of aminophylline were checked against blood blanks collected before administration. The study was further controlled by the administration of placebo suppositories as well as by blood analyses without administration of medication.

Very satisfactory blood levels were obtained with two types of aminophylline suppositories. One type contained 0.5 gm. of aminophylline in a mannitol base, with or without benzocaine. With the use of these suppositories theophylline plasma levels over 500 μg./100 ml. were obtained in 8 of 10 tests; these

blood levels apparently exceed the threshold necessary for aminophylline to exert a diuretic effect. With the second type of suppository, with a buffered carbowax base, levels in excess of 500 μg./100 ml. were obtained in 4 of 6 subjects.

Aminophylline suppositories containing a mannitol base with benzocaine produced sustained plasma levels of theophylline with an approximate average of 650 μg./100 ml. between the fourth and eighth hour after administration and gave the least coefficient of variations in individual responses.

Plasma levels observed in 2 subjects during the first hour after intravenous injection of 0.5 gm. of aminophylline were approximately three times higher than the maximal levels obtained with the same dose of aminophylline in the form of suppositories; these levels were surprisingly well maintained for 2 to 3 hours after injection.

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SUMMARIO IN INTERLINGUA

Concentration de Theophyllina in le Plasma Sanguinee post Administrationes Rectal de Aminophyllina

Aminophyllina esseva administrate rectalmente in le forma de suppositorios a 30 subjectos, e le nivellos plasmatic de theophyllina esseva determinate ab 1 a 8 horas post le administration. Le methodo spectrophotometric ultraviolette de Schack-Waxler esseva usate e se monstrava satisfacentissime. In omne patientes le nivellos plasmatic obtenite post le administration de aminophyllina esseva comparate con specimens de sanguine colligite ante le administration. In ultra, le studio esseva controlate per le administration de suppositorios fictive e etiam per le analyse de sanguine sin medication.

Satisfacentissime nivellos sanguinee esseva obtenite con duo typos de suppositorio a aminophyllina. Un typo contineva 0,5 mg aminophyllina in un base de mannitol, con o sin benzocaina. Con isto, nivellos plasmatic de theophyllina de plus que 500 μg per 100 ml esseva obtenite in 8 inter 10 tests. Tal nivellos sanguinee excede apparentemente le limine necessari proque aminophyllina pote exercer un effecto diuretic. Con le secunde typo de suppositorio, in que se usava un base de Carbowax tamponate, nivellos de plus que 500 μg per 100 ml esseva obtenite in 4 inter 6 subjectos.

Suppositorios de aminophyllina, continente un base de mannitol con benzocaina, resultava in continue nivellos plasmatic de theophyllina de un valor median de circa 650 μg per 100 ml inter le quarte e octave hora post le administration. Illos monstrava le plus basse coefficiente de variationes in le responsas individual.

Le nivellos plasmatic observate in duo subjectos durante le prime hora post le injection intravenose de 0,5 mg aminophyllina esseva circa tres vices plus alte que le nivellos maximal obtenite per le mesme dose de aminophyllina administrate in le forma de suppositorios. Iste nivellos esseva surprendentemente stabile pro 2 a 3 horas post le injection.

THE EFFECTS OF THYROTROPIN AND DESICCATED THYROID UPON HYPOTHYROIDISM WITH GOITER*†

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While the combination of thyroid enlargement and increased thyroid uptake of radioactive iodine is usually diagnostic of hyperthyroidism, there has been increasing recognition of syndromes in which these findings are associated, not with hyper-, but with hypothyroidism. At least 3 distinct types of histologic alteration of the thyroid have been described with this triad of hypothyroidism, goiter, and increased I^{131} uptake.

The so-called "goitrous cretins" of highly endemic goiter regions have been demonstrated to have an avid thyroid uptake of I^{131}, a phenomenon attributed to the iodine deficiency[15]. Such glands may become very large, multinodular, and contain cysts, fibrosis, and colloid-filled follicles of varying size[4]. These glands are reported to regress little with thyroid substitution therapy[12], probably due to the presence of irreversible changes.

Certain hypothyroid children in nonendemic areas are found to have goiters; this disorder tends to be familial, with considerable variation in the goiter size and the severity of the hypothyroidism. The glands of these patients also accumulate abnormally large amounts of I^{131} [3,5,6,9,11,14,16]. Unlike the goiters of endemic areas the histologic picture of these glands is described as that of intense hyperplasia[3,16]. This disorder has been attributed to inborn defects in the synthesis of thyroid hormone.

Recently, still another type of histologic change, lymphocytic thyroiditis, has been found associated with goiter, increased thyroid uptake of I^{131}, and evidence of hypothyroidism. Gribetz, Talbot and Crawford[2] described 6 such children who had a wide range of 48-hour I^{131} uptakes and serum levels of protein-bound iodine (PBI), one of whom had evidence of hypothyroidism. Skillern and his co-workers recently reported a series of patients with the syndrome of thyroid failure coincident with goiter and the biopsy finding of

*Presented in part at the annual meeting of the Midwestern Section of the American Federation for Clinical Research, October 28, 1954, and in the abstracts of the Central Society for Clinical Research[10].

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struma lymphomatosa[13]. In many of their cases an active iodide trapping mechanism was present, but response to thyrotropin (TSH) administration was poor, as judged by changes in the thyroid I^{131} uptake. Thyroid replacement therapy was found to be effective in reducing goiter size.

In the course of performing TSH tests[8] upon suspected hypothyroids over a 2-year period in this institution, 7 cases of hypothyroidism with goiter have been encountered. One was briefly discussed in a previous report[8]. The present communication describes these cases and their responses to TSH and desiccated thyroid.

Clinical Cases. Table 1 summarizes the clinical features of the patients studied. Six were children, and one was an adult; all were from different families. Although each patient had evidence of hypothyroidism, its time of onset and severity varied. Four cases had hypothyroidism which had been present since infancy, one had hypothyroidism at the age of 4 which probably dated back to infancy; one had her symptoms begin at age 9, and another at age 47. In 3 instances hypothyroidism had been detected before the existence of thyroid enlargement was noted. All had goiters, varying in size from small to medium, but none had attained large, disfiguring dimensions. There was no history of iodine deficiency or ingestion of goitrogens, and in only 2 patients was there a family history of thyroid dysfunction.

Histologic examination was not performed on any of these glands, but it appears likely that at least 4 (Cases 1, 3, 4, and 5), and probably also Cases 2 and 6 were due to inborn defects in the ability to form thyroid hormone, while Case 7 acquired such a defect later, possibly due to chronic lymphocytic thyroiditis.

Methods of Study. The responsiveness of all 7 patients to a single injection

TABLE 1.—CLINICAL FEATURES OF HYPOTHYROIDISM WITH GOITER

Case Number	Age Years*	Age, Diagnosis of Hypothyroidism	Race	Sex	Family History Thyroid Abnormality	Clinical Findings	BMR % Untreated	Cholesterol mg./100 ml. Untreated
1	2.5	5 weeks	W	M	No	Moderate goiter, large tongue**		129***
2	4	4 years	C	M	No	Retarded development and bone age small goiter		384
3	7	Birth	W	F	Yes	Retarded development, small goiter		
4	9	6 months	C	F	No	Retarded mental and bone ages, small goiter detected age four		701
5	11	3 months	W	F	No	Umbilical hernia, small goiter that enlarged off treatment	−37	284
6	12.5	9 years	W	F	Yes	Decrease in mental and physical activity, moderate goiter	−11	267
7	47	47 years	W	F	No	Rheumatoid arthritis, thick tongue, puffy eyes, dry skin, small goiter	−18	452

* At time of study. ** At time of original diagnosis. *** This is considered an elevated level for the age of the patient (4 weeks).

of TSH, a measure of thyroid reserve, was tested by a previously reported technique[8]. In brief, this consists of comparing both the PBI* and the 3-hour thyroid uptake of I^{131} before and 24 hours after a single intramuscular injection of 5 units of TSH**. In 4 patients the effects of varying comparison Table 2 also presents the data on normal adults, primary hypothyroids, and patients with nontoxic diffuse goiters. All 4 untreated patients exhibited definitely elevated 3-hour thyroid I^{131} uptakes, without significant further increase in uptake after TSH. Two of the PBI's were in the hypo-

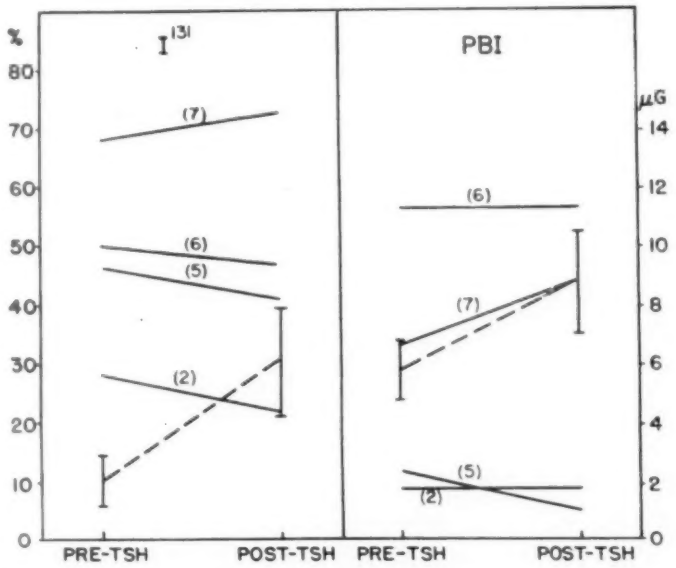

Fig. 1.—Thyrotropin tests in untreated hypothyroidism with goiter. The left ordinate represents the three-hour thyroid I^{131} uptake, expressed as per cent of the administered tracer dose. The right ordinate represents the serum protein-bound iodine, micrograms per 100 ml. The abscissa indicates the pre- and post-thyrotropin values, which are connected with a line, the slope of which indicates the degree of response to thyrotropin. The dotted lines connect the mean and standard deviation of a group of 12 normal adults tested, and the patients are identified by their case numbers.

doses of desiccated thyroid administration were followed, and one case was given a trial of potassium iodide therapy.

Results. Four of the 7 patients (Cases 2, 5, 6, and 7) were seen before treatment had been given. The results of their TSH tests are listed in Table 2 and Fig. 1. For purpose of thyroid range, one was clearly elevated, and one was within normal limits. Only in this last patient (Case 7) did the PBI rise significantly following TSH administration.

In contrast to the definite elevation of the 3-hour I^{131} uptakes in all 4 patients, the 24-hour uptakes ranged from 42% to 69% of the tracer dose

*Performed in duplicate by a modification of Barker's method[1].

**Generously supplied by Dr. Richard A. Carey of the Armour Laboratories.

* At time of study. ** At time of original diagnosis. *** This is considered an elevated level for the age of the patient (4 weeks).

TABLE 2.—THYROTROPIN TESTS IN HYPOTHYROIDISM WITH GOITER COMPARED WITH OTHER CONDITIONS

	Thyroid gm./day	Thyroid I^{131} Uptake, % Tracer Dose: Three-hour Uptake: Pre-TSH	Three-hour Uptake: Post-TSH	Three-hour Uptake: Change	24 Hour	PBI, μg./100 ml.: Pre-TSH	Post-TSH	Change
12 normal adults*	0	10.1 ± 4.1	30.5 ± 9.6	+20.4 ± 7.8	29.3 ± 6.3	5.8 ± 1.0	8.9 ± 1.7	+ 3.1 ± 1.1
6 primary hypothyroids*	0	2.1 ± 0.9	1.5 ± 1.2	— 0.6 ± 0.7	2.9 ± 2.4	1.5 ± 1.4	1.3 ± 1.6	— 0.2 ± 0.7
8 simple nontoxic goiters*	0	12.8 ± 6.1	32.9 ± 10.2	+20.1 ± 5.7	31.0 ± 9.0	5.3 ± 0.9	7.7 ± 2.1	+ 2.4 ± 1.5
		Hypothyroidism with Goiter						
Patient	Thyroid gm./day	Pre-TSH	Post-TSH	Change	24 Hour	Pre-TSH	Post-TSH	Change**
1	032	22.6	46.8	+24.2	23.8	4.5	6.2	+ 1.7
2	0	28.2	22.0	— 6.2	42.0	1.8	1.8	0
3	064	18.9	18.0	— 0.9	4.8	4.2	4.6	+ 0.4
4	0.1	49.4	53.3	+ 3.9	34.3	2.2	2.8	+ 0.6
	0.16	26.6	20.4	— 6.2	11.2	2.8	3.7	+ 0.9
5	0	46.5	41.0	— 5.5	49.6	2.4	1.0	— 1.4
	0.1	29.9	37.1	+ 7.2	33.6	3.7	4.2	+ 0.5
6	0	50.3	46.7	— 3.6	61.9	11.3	11.4	+ 0.1
	0.064	15.1	38.2	+23.1	25.8	9.2	9.3	+ 0.1
7	0	68.2	72.8	+ 4.6	69.3	6.7	8.9	+ 2.2
	0.032	9.7	21.6	+11.9	28.5	5.8	7.7	+ 1.9

* Mean ± standard deviation.

** An increase of more than 1.0 μg. is probably a significant difference.

given, two being within the upper range of normal.

Patient 6 is of particular interest in that she had an abnormally high PBI level associated with the presence of hypothyroidism. A summary of her case follows:

When first seen in 1953, the patient was a well-developed and nourished, rather quiet, 11-year-old girl. Two years prior to study at the age of 9, a goiter had been noticed, and one year prior to examination there had been a marked deterioration of mental ability, her personality changing from very alert to sluggish. During the 6 months preceding study the goiter had undergone obvious further enlargement. There were no other symptoms of hypothyroidism. The initial laboratory findings are listed in Table 1. As seen in Table 2 and Fig. 1, the 3-hour and 24-hour radioactive iodine uptakes were abnormally high, as was the PBI. TSH produced no rise in these already elevated levels. Two hundred milligrams of iodide (as saturated solution of potassium iodide) were then given daily; within a month she was more sluggish, and the goiter had undergone further enlargement. These adverse effects were so marked that the patient's mother discontinued the iodide before repeat tests could be obtained. Desiccated thyroid, 0.064 gm. daily, was then given. Clinical improvement was marked. The patient became bright and alert, and within 6 months there was a 7 cm. increase in height, the serum alkaline phosphatase rising from 4.6 to 12 Bodansky Units. Hence, the presence of mild hypothyroidism was confirmed by the response to thyroid therapy. Furthermore, there was a definite recession in goiter size.

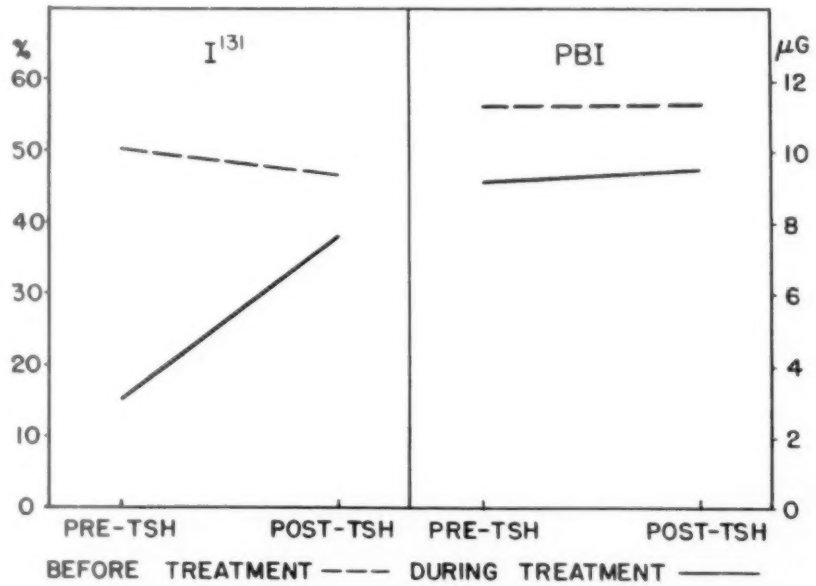

Fig. 2.—The effect of thyroid treatment upon the thyrotropin test in hypothyroidism with goiter, Case No. 6. The construction of the chart is the same as Fig. 1. The dashed lines represent the test before treatment, and the solid lines the during-treatment test.

At this time the TSH test was repeated, and a comparison with the pre-therapy findings is seen in Table 2 and Fig. 2. It may be seen that thyroid administration resulted in a significant fall in the pre-TSH I^{131} uptake, and injection of TSH was now followed by a rise in this index. The PBI had been *lowered* toward normal, but it still did not rise following TSH.

In two other patients (Cases 5 and

7) the effect of desiccated thyroid upon I^{131} uptakes was similar (Table 2); a decrease in the pre-TSH level occurred and responsiveness to stimulation became evident. Patient 2 did not return for follow-up studies. In Patient 5 the PBI rose to normal, and in Patient 7 with a normal initial level it remained normal and again increased following TSH. Thus, thyroid therapy in this disorder caused the abnormal findings to return toward normal regardless of whether they were elevated or depressed. Once thyroid treatment was begun the goiters regularly decreased in size.

Three patients were first seen after replacement therapy had been given for several years. Their condition was still manifest by goiter, elevated I^{131} uptakes, and low PBI levels, reflecting inadequate dosage of thyroid (Table 2). In Patient 4 examination after increasing the dose of thyroid revealed decrease in the goiter and lowering of the I^{131} uptake. The lack of significant rise in PBI, and the continued failure of TSH administration to significantly affect either the PBI or I^{131} uptake suggested the need for a further increase in thyroid substitution therapy.

Discussion. Since neither iodine deficiency nor ingestion of goitrogens could be implicated in any of these cases, it seems probable that they represent either the type of thyroid dysfunction associated with intense hyperplasia or lymphocytic thyroiditis. Although proof is lacking in the absence of biopsy material, the 5 younger children in the series seem more characteristic of the former condition. In Patient 6 the fact that her sister had a goiter and the evidence that she produced an abnormal iodinated compound (*vide infra*), an observation that has not been reported with lymphocytic thyroiditis, suggests that her case also may represent an inborn defect in thyroid hormone synthesis. One might postulate that this patient's thyroid gland produced sufficient amounts of effective thyroid hormone until the needs of oncoming puberty exceeded its capacity, thus causing thyroid enlargement and the clinical symptoms of hypothyroidism.

The possible underlying physiologic abnormalities in this disorder have been discussed by others[6,11,16,17]. In all cases appropriately studied, the preservation of thyroid iodide trapping has been demonstrated by a rapid and large thyroid uptake of I^{131}. In some cases defective protein-binding of the trapped iodide has been implicated by the rapid discharge of accumulated thyroidal iodide^{131} with potassium thiocyanate and by low levels of serum PBI[14,16].

In other cases of this disorder the disappearance of I^{131} from the thyroid has been less rapid, and thiocyanate has been ineffective in discharging radioactivity from the gland[3,11], indicating that protein-binding of the trapped iodide has occurred. Under these circumstances the hypothyroidism may be explained either by insufficient protein-binding resulting in decreased production of thyroid hormone, or alternatively by aberrant protein-binding resulting in production of iodinated compounds that are relatively inert. Significant circulating PBI^{131}, *with*[5,17] and *without*[17] circulating thyroxine has been reported, suggesting that either mechanism may operate. Patient 6 of the present series, who was hypothyroid despite an elevated PBI, seems to be a clear example of the latter mechanism. Of interest in this regard are the reports of McGirr and Hutchison[6,11] that the serum of one of their patients was subjected to chromatographic analysis and an unidentified iodinated protein was found that was neither thyroxine nor tri-

iodothyronine. It has not yet been feasible to perform similar tests on the sera of the present patients. In a more recent report Ingbar and Freinkel[7] have described a woman who may have had a similar defect in thyroid hormone synthesis. Their patient was myxedematous with a low PBI, but her 24-hour I^{131} uptakes ranged between 40 and 50%. Labelled thyroxine turnover studies revealed a normal rate of hormone production, but an abnormally low rate of thyroxine degradation. These workers state that preliminary studies indicated that this patient's thyroid gland was producing and releasing both thyroxine and a less metabolically active iodinated compound.

The intense thyroid hyperplasia found in this syndrome is consistent with a marked action of TSH. The failure of the 4 untreated patients to respond to injections of this hormone supports the impression that their thyroid glands were already under maximal stimulation from endogenous thyrotropin. The effect of thyroid replacement therapy in lowering the I^{131} uptake, lowering the PBI when it is elevated, decreasing the goiter size, and rendering the thyroid gland responsive to exogenous TSH is well explained by a decrease in pituitary output of TSH.

A review of the clinical features of the present series of 7 patients, as well as previously reported cases of hypothyroidism with goiter, reveals that the disordered thyroid function may be present at birth or appear after years of apparently adequate thyroid hormone production. The goiters may vary considerably in size, as does the degree of hypothyroidism. In contrast to the experience of others, the majority of the cases presented in this report were apparently sporadic rather than familial.

It seems likely that this syndrome is more common than previously realized. In view of the fact that the 24-hour I^{131} uptakes in this condition may fall within the normal range, it is suggested that patients presenting the combination of symptoms of hypothyroidism and a palpable thyroid gland be screened with an early (3-hour) as well as a 24-hour uptake. Elevated early values in the absence of goitrogens or iodine deficiency should suggest the diagnosis.

Early detection and adequate treatment of this disorder will not only prevent the effects of hypothyroidism, but also the development of large goiters which later might require surgical removal.

Summary. Seven patients, 6 children and one adult, with the syndrome of hypothyroidism and goiter were studied by means of the thyroid I^{131} uptake and the level of serum protein-bound iodine (PBI), and the response of these indices to thyrotropin (TSH) administration. Although elevated 3-hour I^{131} uptakes were found in all cases, there was considerable variation in the 24-hour uptakes. The PBI's ranged from below normal to the definitely elevated value of 11.3 μg. per 100 ml. In all untreated cases TSH injection had no effect upon the I^{131} uptake, and in only one patient was there a significant increase in PBI following this stimulus. Thyroid replacement therapy regularly relieved the symptoms of hypothyroidism, lowered the I^{131} uptake, caused a return of the PBI toward normal, and resulted in a decrease in the thyroid enlargement.

It is postulated that this syndrome is due to defective thyroid hormone synthesis, causing an augmented pituitary output of TSH, with consequent goiter formation and lack of response to exogenous stimulation in untreated cases.

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SUMMARIO IN INTERLINGUA

Le Effectos de Thyrotropina e de Desiccate Thyroide Super Hypothyroidismo con Struma

Septe patientes, 6 juveniles e un adulto, con le syndrome de hypothyroidismo con struma esseva studiate per medio de determinationes del absorption thyroide de iodo radioactive e del nivello seral de iodo ligate a proteina, e del responsa de iste indices al administration de thyrotropina. Le absorption de iodo radioactive post 3 horas esseva augmentate in omne casos, sed post 24 horas illo monstrava considerabile variationes. Le nivellos seral de iodo ligate a proteina variava inter valores subnormal e le clarmente elevate valor de 11,3 μg per 100 ml. In omne non-tractate casos, le injection de thyrotropina habeva nulle effecto super le absorption de iodo radioactive. In un sol caso iste stimulo esseva sequite per un significative augmento del nivello seral de iodo ligate a proteina. Therapia a substitution thyroide habeva regularmente le effecto de alleviar le symptomas de hypothyroidismo, de reducer le absorption de iodo radioactive, de causar un retorno del nivello seral de iodo ligate a proteina verso valores normal, e de diminuer le allargamento thyroide.

Nos postula que le syndrome es debite a un defecto del synthese de hormon thyroide e que isto causa un augmentate secretion de thyrotropina con le formation consequente de struma e non-reaction al stimulation exogene in non-tractate casos.

A STUDY OF THE "FLAT" ORAL GLUCOSE TOLERANCE CURVE AND ITS RELATION TO RATE OF EMPTYING OF THE STOMACH

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Failure of the blood sugar to rise normally after the ingestion of a test dose of glucose has been observed in a variety of clinical conditions. Such "flat" curves of the blood sugar have been reported in patients with hypopituitarism, anorexia nervosa, Addison's disease, myxedema, and steatorrhea[9]. In the course of routine inspection and analysis of oral glucose tolerance tests we were surprised at the frequency with which flat blood sugar curves were found in the absence of any of the clinical syndromes commonly associated with such curves. We selected 26 patients in whom no obvious explanation for the flat blood sugar curve was apparent, and studied their carbohydrate tolerance in detail. We defined a flat blood sugar curve as one in which the maximum rise of venous blood sugar in a 3-hour period after a standard oral dose of glucose was less than 30 mg. per 100 ml.

Methods. The oral glucose tolerance test was performed after a fast of at least 12 hours, with the patient on an unrestricted diet. The test dose of glucose was 1 gm. per kilogram of standard body weight, dissolved in water (7 ml. per gm. of glucose) and taken by the patient within a 5-minute period. Blood sugars were determined in the fasting state, and at intervals of 30, 60, 120, and 180 minutes. For the intravenous glucose tolerance test, a fixed dose of 50 ml. of 50% glucose solution was injected over a period of 2 minutes. Blood sugars were determined in the fasting state, and at intervals of 5, 15, 30, 60 and 90 minutes thereafter. At least one oral test was done in each patient, with about 60 ml. of a mixture of equal parts of barium and water added to the glucose solution, in order that the rate of emptying of the stomach could be observed fluoroscopically. In many of the patients,

*Dr. Nichols was at the University of Chicago when he participated in this work.

TABLE 1

Blood Glucose (mg./100 ml.)
Serum Inorganic Phosphorus (mg./100 ml.)

Patient	*Date*	*Type of Test*	*Fasting*	*5 min.*	*15 min.*	*30 min.*	*1 hr.*	*90 min.*	*2 hrs.*	*3 hrs.*	*Remarks*	*Gastric Emptying*	*Diagnosis*
E.R.	6–13–50	Oral	74	..	..	93	..	..	78	61	Venous	Not done	Tinea rubrum
	1–11–51	Intravenous	99	212	171	129	85	135	..	..	Venous	..	
	3–20–51	Oral	75	..	..	96	95	..	76	62	Venous	Normal	
S.G.	8–15–50	Oral	83	..	..	88	..	..	78	76	Venous	Not done	Functional bowel distress
	2–13–51	Oral	79	..	..	101	73	..	53	62	Venous	Normal	
E.J.	4–11–50	Oral	85	..	..	83	..	..	88	65	Venous	Not done	Duodenal ulcer (non-stenosing)
	12– 5–50	Oral	74	..	..	81	77	..	77	42	Venous	Normal	
	2–15–51	Intravenous	78	249	210	173	112	93	..	..	Venous	..	
	5–22–51	Oral	82	..	..	119	94	..	58	58	Venous	Not done	
	..	..	91	..	..	145	110	..	71	65	Capillary	..	
	..	..	4.0	..	..	2.7	2.7	..	2.7	3.1	Phosphorus	..	
A.G.	1– 9–50	Oral	67	..	..	67	..	..	71	48	Venous	Not done	Unexplained fatigue
	11–14–50	Oral	85	..	..	84	75	..	67	78	Venous	Normal	
	5– 9–51	Oral	72	..	..	102	80	..	71	62	Venous	Not done	
	..	..	90	..	..	140	117	..	97	87	Capillary	..	
	..	..	3.6	..	..	3.0	3.1	..	3.1	3.6	Phosphorus	..	
A.Z.	11–29–49	Oral	81	..	..	99	..	..	64	67	Venous	Not done	Anemia due to iron deficiency
	11–14–50	Oral	68	..	..	84	46	..	71	60	Venous	Normal	
	5–22–51	Oral	83	..	..	112	65	..	67	73	Venous	Not done	
	..	..	87	..	..	138	118	..	88	81	Capillary	..	
	..	..	2.7	..	..	2.6	2.5	..	2.5	2.7	Phosphorus	..	
J.S.	10–20–50	Oral	73	..	..	85	..	..	69	69	Venous	Not done	No disease
	1–16–51	Oral	64	..	..	103	89	..	80	64	Venous	Delayed	
	5– 8–51	Oral	82	..	..	120	119	..	84	82	Venous	Normal	
	..	..	98	..	..	136	152	..	119	91	Capillary	..	
	..	..	3.6	..	..	3.3	3.0	..	2.7	2.9	Phosphorus	..	
R.J.	2–15–49	Oral	78	..	..	95	..	..	68	88	Venous	Not done	No disease
	2– 6–51	Oral	88	..	..	107	69	..	70	79	Venous	Delayed	
	..	..	96	..	..	185	100	..	78	89	Capillary	..	
	..	..	3.7	..	..	3.5	2.9	..	2.3	2.7	Phosphorus	..	
	5–15–51	Oral	83	..	..	115	87	..	99	81	Venous	Delayed	
	..	..	86	..	..	129	103	..	103	89	Capillary	..	
	..	..	3.7	..	..	3.2	2.9	..	2.7	3.1	Phosphorus	..	
E.H.	..	Oral	65	..	..	65	..	..	54	64	Venous	Not done	Obesity
	3– 6–51	Oral	65	..	..	70	52	..	53	71	Venous	Normal	
	..	..	89	..	..	128	99	..	74	72	Capillary	..	
	6– 5–51	Oral	70	..	..	96	64	..	63	59	Venous	Not done	
	..	..	81	..	..	137	118	..	91	70	Capillary		
	..	..	3.0	..	..	2.7	2.4	..	2.7	3.1	Phosphorus		
H.G.	9–16–48	Oral	58	..	..	75	73	..	55	57	Venous	Not done	Regional enteritis (in remission)
	1– 3–51	Oral	78	..	..	74	54	..	78	78	Venous	Normal	

			89	..	..	128	99	..	74	72	Capillary	..	
	6- 5-51	Oral	70	..	..	96	64	..	63	59	Venous	Not done	
	..	..	81	..	..	137	118	..	91	70	Capillary	..	
	..	..	3.0	..	..	2.7	2.4	..	2.7	3.1	Phosphorus	..	
H.G.	9-16-48	Oral	58	..	..	75	73	..	55	57	Venous	Not done	Regional enteritis (in remission)
	1- 3-51	Oral	73	..	..	74	54	..	73	58	Venous	Normal	
	..	..	94	..	..	133	105	..	117	92	Capillary	..	
	6- 5-51	Oral	73	..	..	87	51	..	76	74	Venous	Not done	
	..	..	81	..	..	118	107	..	115	97	Capillary	..	
	..	..	3.6	..	..	3.3	2.9	..	..	3.4	Phosphorus	..	
G.B.	7-20-50	Oral	74	..	..	72	..	..	96	56	Venous	Not done	(1) Functional bowel distress
	4- 3-51	Oral	66	..	..	84	73	..	87	70	Venous	Normal	
	..	..	96	..	..	140	129	..	125	94	Capillary	..	
	..	..	3.2	..	..	2.8	3.2	..	3.2	3.2	Phosphorus	..	
	6- 5-51	Oral	64	..	..	85	86	..	52	43	Venous	Not done	(2) Meningioma in region of optic chiasm, previously excised
	..	..	84	..	..	130	138	..	103	69	Capillary	..	
	..	..	2.9	..	..	2.9	2.7	..	2.8	3.0	Phosphorus	..	
J.N.	7- 6-48	Oral	82	..	..	94	..	..	80	59	Venous	Not done	No disease
	12-19-50	Oral	78	..	..	83	65	..	71	69	Venous	Normal	
	5- 1-51	Oral	80	..	..	82	61	..	72	66	Venous	Not done	
	..	..	89	..	..	127	83	..	108	84	Capillary	..	
	..	..	3.2	..	..	2.8	3.0	..	2.8	3.1	Phosphorus	..	
J.E.	3-28-50	Oral	81	..	..	103	..	..	84	89	Venous	Not done	Major convulsions
	1- 9-51	Oral	71	..	..	112	83	..	74	68	Venous	Delayed	
	5-15-51	Oral	73	..	..	91	55	..	81	74	Venous	Normal	
	..	..	79	..	..	112	75	..	95	75	Capillary	..	
	..	..	3.5	..	..	3.4	3.3	..	3.2	3.4	Phosphorus	..	
J.B.	5-15-50	Oral	69	..	..	88	..	..	58	64	Venous	Not done	No disease (father diabetic)
	12-19-50	Oral	75	..	..	96	65	..	65	68	Venous	Delayed	
	5-15-51	Oral	75	..	..	89	80	..	85	64	Venous	Delayed	
	..	..	80	..	..	129	108	..	97	71	Capillary	..	
	..	..	3.4	..	..	3.3	3.1	..	3.3	3.4	Phosphorus	..	
L.R.	5- 3-49	Oral	81	..	..	96	..	..	75	71	Venous	Not done	Functional bowel distress
	1-16-51	Oral	74	..	..	75	75	..	74	50	Venous	Delayed	
	5-15-51	Oral	75	..	..	85	71	..	81	62	Venous	Normal	
	..	..	85	..	..	130	111	..	103	74	Capillary	..	
	..	..	3.8	..	..	3.6	3.6	..	3.5	4.1	Phosphorus	..	
I.N.	9-21-48	Oral	78	..	..	96	..	..	83	53	Venous	Not done	(1) Major convulsions
	12-12-50	Oral	66	..	..	89	84	..	70	67	Venous	Normal	
	5-22-51	Oral	60	..	..	182	226	..	140	45	Venous	Not done	(2) Nonspecific ulcerative colitis
	..	..	95	..	..	195	..	..	173	..	Capillary	..	
	..	..	3.1	..	..	2.8	2.7	..	2.3	2.9	Phosphorus	..	
M.L.	1-26-50	Oral	67	..	..	80	..	..	53	65	Venous	Not done	Convulsive state. Etiology unknown
	12- 5-50	Oral	80	..	..	82	60	..	76	82	Venous	Normal	
	3- 8-51	Intravenous	62	193	94	40	30	74	..	..	Venous	..	
	6- 5-51	Oral	68	..	..	49	59	..	59	66	Venous	Not done	
	..	..	82	..	..	97	92	..	88	85	Capillary	..	
	..	..	3.3	..	..	3.1	3.0	..	3.2	3.4	Phosphorus	..	

capillary as well as venous blood sugar together with serum phosphorus were determined simultaneously.

Venous blood glucose was determined by the Somogyi-Shaffer-Hartman method[10] on unlaked blood filtrates prepared by the method of Folin[2]. Normal values obtained by this method range from 60 to 90 mg. per 100 ml. Capillary blood glucose was determined according to the method of Miller and Van Slyke[7], which gives normal values of from 70 to 100 mg. per 100 ml. All blood chemical determinations in tests subsequent to the original one in each patient were performed in duplicate.

Results. When the oral glucose tolerance test was repeated in each of the 26 patients, the test was normal in 10. These 10 patients were not subjected to further study. The results of tests in the remaining 16 patients are given in Table 1.

In 2 patients (E.R. and S.G.), both of whom had persistently flat blood sugar curves, it was not possible to study serum inorganic phosphorus changes or capillary blood sugar. E.R. had a normal intravenous tolerance test and no delay in gastric emptying. In S.G. no intravenous tolerance test was done, and again there was no delay in gastric emptying.

In 5 patients (E.J., A.G., J.S., A.Z., and R.J.) final studies of venous and capillary blood sugar curves after oral glucose were normal, although in 4 of these (E.J., A.G., A.Z., and R.J.) two previous oral tests had shown flat blood sugar curves. Gastric emptying was normal in association with flat blood sugar curves on three occasions (E.J., A.G. and A.Z.), and delayed in association with normal blood sugar curves on two occasions (J.S. and R.J.). The maximum fall of serum inorganic phosphorus in association with normal blood sugar curves in these patients varied from 7% to 38% but, in all except patient A.Z., was greater than 15%.

In 7 patients (E.H., H.G., G.B., J.N., J.E., J.B., and L.R.) oral glucose administration produced flat venous blood sugar curves, and capillary blood sugar curves with rather low peaks. Gastric emptying was normal in 4 of these patients (E.H., H.G., G.B. and L.N.). In patient J.B., it was consistently delayed; in J.E. and L.R., delayed on one occasion and normal on another. The maximum fall of serum inorganic phosphorus varied from 8 to 20%. In only 2 of these patients (E.H. and H.G.) did it exceed 15%.

In one patient (I.N.) a flat blood sugar curve changed to a curve of the diabetic type at the time of the final study. Gastric emptying was normal, and the maximum fall in serum phosphorus was 26%.

In only one patient (M.L.) of the entire series were the curves of both venous and capillary blood sugar persistently flat. In this patient the maximum rise in blood sugar after intravenous glucose was definitely subnormal. Gastric emptying was normal. The maximum fall in serum phosphorus was 9%.

Discussion. It was hoped that the study of gastric emptying would help to account for at least some if not most of the flat blood sugar curves in our series, since others have stated that delayed emptying of the stomach due to frank pyloric obstruction causes a flat blood sugar curve[1]. Our results, however, were inconsistent. Delay in gastric emptying was found nearly as often with normal blood sugar curves as with flat ones, and conversely many flat curves were found in association with normal gastric emptying. In our patient other mechanisms than simple delay in passage of glucose from stomach to small bowel must be sought to explain the flat blood sugar curves.

The most persistently abnormal pattern in the present series was the association of flat venous blood sugar

curves with capillary blood sugar curves that showed a distinct peak at ± 130 mg. per 100 ml. (7 patients). In attempting to explain this apparent discrepancy, it must be recalled that the capillary blood sugar represents the concentration of glucose in the arterial blood at the finger tip after the liver has removed what it will, and that the venous blood sugar determined on a sample drawn at the antecubital space represents that same value minus the glucose that the muscles of the hand and arm have withdrawn.

In view of these facts, there are three possible explanations for the coexistence of a flat curve as determined on venous blood and a normal curve as determined on capillary blood:

1. Intestinal absorption might be retarded, while the disposal of glucose by the liver and muscles is normal. The resulting, and possibly only moderate, depression of the capillary blood sugar curve might be sufficient to render the venous curve relatively flat.

2. Intestinal absorption and peripheral utilization might be normal, while removal of glucose by the liver is accelerated. This would be expected to have the same effect as in the first instance.

3. Intestinal absorption and hepatic disposal might be normal, with increased utilization by the muscles. In this event the capillary curve would be normal and the venous depressed.

Obviously, combinations of these factors might exist.

The behavior of the serum inorganic phosphorus suggests impaired absorption as the best explanation in the cases under discussion. Forsham and Thorn[3] have stated that normally these values fall from 9 to 39% (average 25%) below the initial level following intravenous administration of glucose, and Hartman and Bolliger[5] have found no difference in the decline of serum phosphorus when glucose was given orally instead of intravenously. In 5 of our 7 patients showing flat venous and normal capillary curves the maximum fall was less than 15% and in the other two it was 19 and 20% respectively. If, as is proposed by Forsham and Thorn, the decrease is proportional to the rate of utilization of glucose, then the small decrements observed in our patients would argue against an increased utilization. And if, as shown by Hanes and others[4], defective absorption of glucose, as in sprue, is associated with minimal changes (8 to 12%) in phosphorus levels, then our data would point toward a disturbance of intestinal function. This conclusion, however, should be accepted only with reservations, since serum phosphorus levels are doubtless influenced by many factors, among them being the occurrence of phosphorylating processes, after the ingestion of glucose, almost simultaneously in three different places: the intestinal mucosa, the liver and the muscles.

Summary. Carbohydrate tolerance was studied in 26 patients who were found to have flat blood sugar curves after an oral glucose tolerance test. The rate of emptying of the stomach was observed fluoroscopically by the simultaneous administration of barium with the glucose.

It was not possible to demonstrate a consistent relation between delay in gastric emptying and the occurrence of a flat blood sugar curve. A defect in intestinal absorption as the cause of persistent depression of blood sugar curves is suggested by analysis of the data presented.

In 15 of the original group of 26 patients, a flat blood sugar curve later became normal. This points up the value of repeating the test before one attaches diagnostic significance to it.

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SUMMARIO IN INTERLINGUA

Un Studio del "Applattate" Curva del Toleration de Glucosa Oral e Su Relation al Tempo del Vacuation Gastric

Le toleration de hydratos de carbon esseva studiate in 26 patientes in qui applattate curvas de sucro sanguinee habeva essite constatate post tests del toleration de glucosa oral. Le tempo del vacuation gastric esseva observate fluoroscopicamente per le administration de barium simultaneemente con le glucosa.

Il non esseva possibile demonstrar un relation systematic inter retardos del vacuation gastric e le occurrentia de applattate curvas de sucro sanguinee. Le analyse del datos sub mano justifica le these que un defecto del absorption intestinal es le causa del persistente depression del curvas de sucro sanguinee.

In 15 ex le gruppo original de 26 patientes, le applattate curva de sucro sanguinee se normalisava plus tarde. Isto accentua le importantia de repeter le test ante que on attribue a illo un signification diagnostic.

SUMMARIO IN INTERLINGUA

(See page 75 for original article)

Studios del Con- e Disgelation de Erythrocytos Human

Nostre conclusiones es le sequente:

1. Le "Pluronico F-68" e le "Tetronico 707" in concentrationes de 25 pro cento e le "Polyglycoles E-6000 e E-9000" in concentrationes de 20 pro cento protege 94 pro cento de un suspension de erythrocytos human contra hemolyse per rapide con- e disgelation.

2. Agglutination per se non protege le cellulas contra hemolyse per con- e disgelation.

In plus nos propone le sequente hypotheses:

1. Compositos que protege erythrocytos human contra hemolyse per con- e disgelation possede un ligamine polar ab carbon a oxygeno e etiam le oxygeno necessari pro establir un ligamine al hydrogeno del aqua.

2. Iste compositos pote esser efficace in prevenir hemolyse sin entrar in le erythrocytos.

3. Le massa per se del polymero non protege le cellulas contra hemolyse per con- e disgelation.

SOME STUDIES ON FREEZING AND THAWING HUMAN ERYTHROCYTES*

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IN 1950, A. U. Smith[12] discovered that glycerol will protect both spermatozoa and human erythrocytes from being destroyed by freezing and thawing. The theoretical and practical implications of this discovery were rapidly seen by many different workers. One of us had been working on the stability of colloids to freezing and thawing, and was therefore anxious to test whether some of the general conclusions drawn from relatively simple systems would hold for more complex living systems.

Material and Methods. The initial experiments were designed to observe the rate of freezing and to determine the degree of supercooling and fractional freezing.

The experimental procedure was as follows: 3 ml. of the material to be tested was placed in a 7 ml. pyrex test tube. The test tube was then placed in an ice bath and kept there until the contents were frozen. The test tube was then removed from the bath and thawed. Temperatures in the test tubes were measured during this entire procedure by means of a copper-constantine thermocouple connected either to an automatic recording Micro-Max or to a potentiometer. In the latter case readings were taken every 15 seconds. The reference thermocouple was placed in a Dewar Flask containing ice water and solid ice at 0° C. The freezing bath was at −25° C.

The solutions used were 0.9% NaCl, 20% sucrose, 12% gelatine, human plasma, human erythrocytes, and human erythrocytes in 20% sucrose.

The second phase of the work concerned the effectiveness of different media in preventing hemolysis when human erythrocytes were frozen and thawed. The substances tested for protective activity can be divided into 3 major types: inorganic ions, small organic molecules, and large organic polymers.

The experimental procedure was as follows: The solutions were made up to desired strength. To 1.0 ml. of this solution in a 7 × 1 cm. pyrex test tube was added 1.0 ml. of packed human erythrocytes. This suspension was frozen by immersing the test tube in a dry-ice-alcohol bath at −79° C. for 10 minutes. Following this the suspension was thawed by placing the test tube in a water bath at 37° for 10 minutes. The cells were spun down and the supernatant was diluted 200:1 with 0.007 NH_4OH. An unspun unfrozen sample of the same suspension was also diluted 200:1 with 0.007N NH_4OH. The two diluted samples were compared by reading the light absorption at 540 mμ on a photoelectric photometer. The percentage hemolysis was calculated as the ratio of the reading of the supernatant to the reading of the control multiplied by one hundred.

Work on other colloidal systems[4] has indicated that of the inorganic ions, the lithium ion and the fluoride ion, were very active in stabilizing the system and preventing gross changes due to freezing and thawing. Therefore the compounds tested were: a series of sodium salts including the fluoride, chloride, and iodide; and lithium chloride. These salts were tested at two concentrations, 0.15N and 0.30N.

*Aided by a Grant from the United States Public Health Service.

In the field of small organic molecules, recent work[6,7,10,11] on the preservation of erythrocytes in the frozen state has made use of glycerol to prevent hemolysis in the thawed samples. This work was repeated and confirmed in this laboratory as a check on the experimental technique used here. Many other polyoxy compounds such as ethylene glycol and propylene glycol have also been used with some measure of success. Other compounds such as ethylene diamine and ethanolamine have been tried but appear to be inherently too toxic to the erythrocytes.

Prior to our present study no compound has prevented extensive hemolysis due to freezing and thawing unless it is capable of diffusing into the erythrocytes. This leaves unanswered the question as to where the above compounds have their action: inside the cell, outside the cell, or in both positions. High polymers readily lend themselves to settling the question of locus of action, since they will not enter the intact erythrocytes[2].

The effects of series of compounds containing carbon to oxygen bonds, having oxygen atoms available for hydrogen bonding when in aqueous solution, and having a range of molecular weight from 400 to 9000 were studied. These compounds have physico-chemical properties similar to glycerol, and thus could be expected to distort the ice lattice[1]. In addition they should have the physiological property of not being able to diffuse into the erythrocyte[5]. Compounds expected to satisfy these requirements were found in the "Pluronic,"° "Tetronic,"° and "Polyglycol"°° series.

"Pluronics" are condensation products of ethylene oxide on a starting molecule of polyoxypropylene. "Tetronics" are similar to "Pluronics" except that the starting molecule is ethylene diamine. "Polyglycols" are condensation products of ethylene oxide on a starting molecule of ethylene glycol.

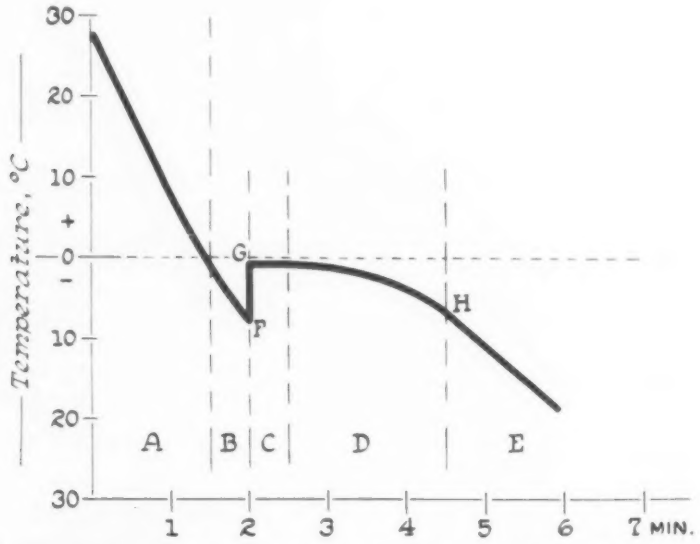

Fig. 1.—Representative temperature-time curve showing supercooling and fractional freezing of a solution immersed in a bath at −25° C.

The following compounds were studied: E-400, E-1,000, E-6,000, and E-9,000 of the "Polyglycol" series; T-707 of the "Tetronic" series; and L-44, L-62, L-64, and F-68 of the "Pluronic" series.

"Pluronic" F-68 is a polymer consisting of 80% ethylene oxide and 20% propylene oxide. It has a mean molecular weight of 7,500. "Pluronic" L-44 and L-64 are compounds of the same general type as "Pluronic" F-68, but have a lower mean molecular weight, a lower percentage of ethylene oxide, and a higher percentage of propylene oxide. "Tetronic"

°Wyandotte Chemical Company.

°°Dow Chemical Company.

707 is similar in molecular weight to "Pluronic" F-68.

Due to the high molecular weight of these polymers their osmotic activity is very small compared to the usual substances tested for erythrocyte permeability. In order to test for erythrocyte permeability, the concentration of polymer was determined in an aliquot of the stock solution of polymer. A second aliquot was then taken and incubated with erythrocytes at room temperature for one day. The red cells were then spun down and the concentration of polymer was determined in the supernatant. A comparison of the two concentrations showed that no polymer had entered the red cell.

Results. The results of the study of the rate of freezing and amount of supercooling are summarized in graphic form. The general form of the graphs obtained is shown in Fig. 1. The graph is divided into 5 distinct portions.

The first region (A) measures the rate of cooling of the liquid material. There is a linear drop of temperature with respect to time, the slope being determined by the temperature differential between the bath and the test tube, the thermal conductivity of the test tube, and the thermal conductivity of the solution. This slope was found to be substantially the same for all the liquids tested, if the experimental conditions were the same. Because this portion of the graph obeyed the classical laws of thermodynamics[3] and seemed to reveal no new information it was not investigated further.

The second region of the graph (B) is the region of supercooling. The supercooling could be eliminated entirely by seeding the solution. Relatively slow cooling leads to a greater degree of supercooling. The point F is the point of maximum supercooling and was never lower than —8.6° C. with human erythrocytes by this experimental technique.

The third region (C) is the area in which there is a plateau, the level of which indicates the freezing point of the solution (G). This freezing point (G) always corresponded to the freezing point calculated from the concentration of osmotically active particles and never coincided with the freezing point of pure water.

The fourth region (D) is an area with a constantly changing slope. The possibility that this varying slope was due to laminar freezing, that is, freezing of the layer of solution nearest the wall of the tube followed by freezing of the next innermost layer, and so forth was ruled out by using test tubes of widely varying diameters and still obtaining essentially the same graph. This changing slope is best explained by the freezing out of solution of pure water. This would result in a mixture of a solid phase of relatively low thermal conductivity and a liquid phase that contained a higher concentration of osmotically active particles with a relatively high thermal conductivity. The varying slope is due to the varying proportions of liquid and solid phase. This phenomenon is termed "fractional freezing." The effect of fractional freezing was least marked with 0.9% NaCl solution, slightly more marked with 20% sucrose solution, more marked with plasma, 12% gelatin, human erythrocytes, and human erythrocytes suspended in 20% sucrose in order of increasing fractional freezing. The curves for human erythrocytes alone and in 20% sucrose were similar and the slope did not become linear again until a temperature of —15° C. was obtained (H). This area (D) is of great theoretical importance.

The last area (E) measures the rate of cooling of the solid material. There is a linear drop of temperature with respect to time, the slope being determined by the temperature differential between the bath and the test tube, the thermal conductivity of the test tube, and the thermal conductivity of

the solid. This slope was found to be substantially the same for all of the materials tested under the same experimental conditions.

In the second phase of this work different media were used to try to prevent freezing-thawing hemolysis.

None of the inorganic salts at the concentrations indicated gave any protection against the freezing-thawing hemolysis of human erythrocytes.

Glycerol was used as a check on our experimental technique. The results obtained were in complete agreement with those stated in the literature[6,7,10,11].

Representative data for the protective effect of the large organic polymers are shown in Fig. 2. The average per cent hemolysis after freezing and thawing is shown in relation to the percentage of polymers in the suspending medium.

It is shown in Fig. 2 that at a concentration of 25% both F-68 and T-707 protect an average of 95% of the erythrocytes against hemolysis. This protective action diminishes as the concentration is reduced. Table 1 shows the range from which the averages for F-68 in Fig. 2 were obtained. Five or more experiments were performed at each concentration listed.

TABLE 1

% Hemolysis	*% F-68*
63–83	5
55–63	10
25–42	15
10–19	20
5–17	22
2– 6	25

In a previous publication[13] it was stated that when erythrocytes which had been treated with high concentration of polymer, frozen and thawed, were diluted with 0.9% NaCl and 0.6% NaCl they exhibited normal fragility. Further studies have shown that erythrocytes treated with high concentrations of polymer but not frozen did exhibit normal fragility on dilution with saline even if the suspensions were kept for 24 hours. It was also found that erythrocytes treated with high concentrations of polymer and then frozen and thawed, exhibit apparently normal fragility for at least the first 5 minutes after dilution with saline. However, if this suspension was allowed to stand for one hour, it was found that the cells were completely hemolyzed at both 0.9% and 0.6% NaCl.

Figure 3 represents a plot of percentage hemolysis versus molecular weight when all of the compounds are glycol and polyglycol analogues. The lowest molecular weight is 62 for ethylene glycol and the highest mean molecular weight is 9,000 for "Polyglycol," E-9,000. It is of interest to note that there is a maximum in the curve at a molecular weight of 400, which is the largest compound tested prior to this study.

The effective concentration of polymer is also the concentration in which a great deal of agglutination of the erythrocytes occurs. A test was therefore set up to determine if agglutination alone will protect the cells from hemolysis on freezing and thawing. Anti-A serum was added to a sample of group A cells until there was gross agglutination of the same order as that which occurred with the addition of the polymers. This sample was then frozen and thawed as above and was found to be 100% hemolyzed after the experimental procedure.

Since a fairly high concentration of polymer was required to be effective in preventing hemolysis it was possible that the mass of the polymer alone was disrupting the ice lattice. A 25% solution of "Polyvinylpyrrolidone," (PVP), a compound which has much

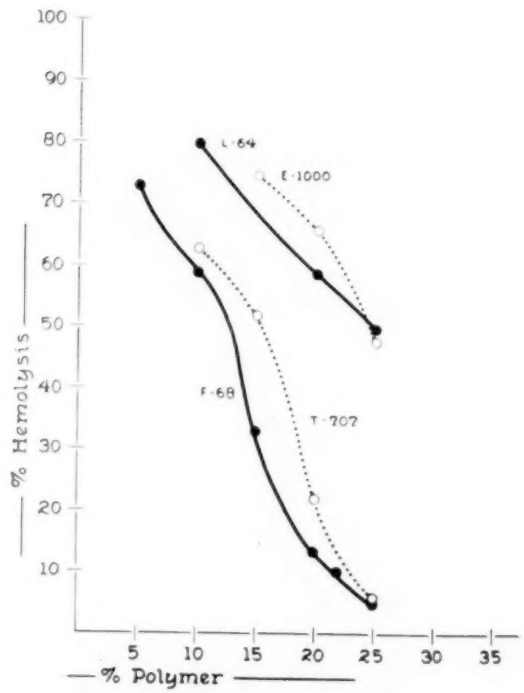

Fig. 2.—Plot of data showing the efficacy of varying concentrations of four polymers in preventing freezing-thawing hemolysis.

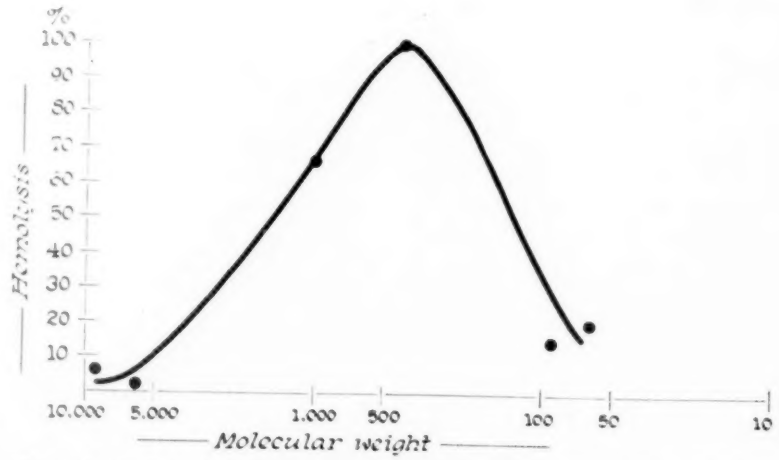

Fig. 3.—The relationship of the molecular weight of different analogues to their prevention of freezing-thawing hemolysis. The concentration of the compounds was kept constant.

less polarity and hydrogen bonding, was then used as the suspending medium. This sample was subjected to the routine freezing and thawing procedure and the sample was found to be 100% hemolyzed.

Discussion. It has been noted that all of the compounds found to be effective in preventing freezing-thawing hemolysis have polar carbon to oxygen bonds. The oxygen in these compounds is also available to bond with the hydrogen of the water molecule, that is, a bond could be formed between the oxygen in the organic solute and the hydrogen of the water solvent[9]. Due to the polar nature of these compounds and the strong hydrogen bonding they exhibit, it would be possible for these compounds to distort the normal ice lattice on rapid freezing of their aqueous solutions[1].

Two major theories of the mechanism of freezing-thawing hemolysis have been described. One, proposed by Lovelock[7,8], states that the freezing-thawing hemolysis of erythrocytes is the result of high salt concentration, that is, over 0.8 m NaCl, caused by the separation of pure ice from the solution. The other theory[13] suggests that freezing-thawing hemolysis results principally from the formation of ice crystals outside the erythrocytes, thus causing mechanical disruption.

In this paper we have given evidence for Lovelock's theory with the time-temperature curves. Part D of these curves shows fractional freezing, as predicted by this theory, which predicts that the lower the temperature, the greater the salt concentration and, therefore the greater the hemolysis. This is called the "salt effect." From Fig. 4A it can be seen that the hemolysis would be zero at 0° C. and increase with decreasing temperature until about —50° C. where there would be 100% hemolysis. Any temperature below —50° C. should lead to 100% hemolysis according to this theory.

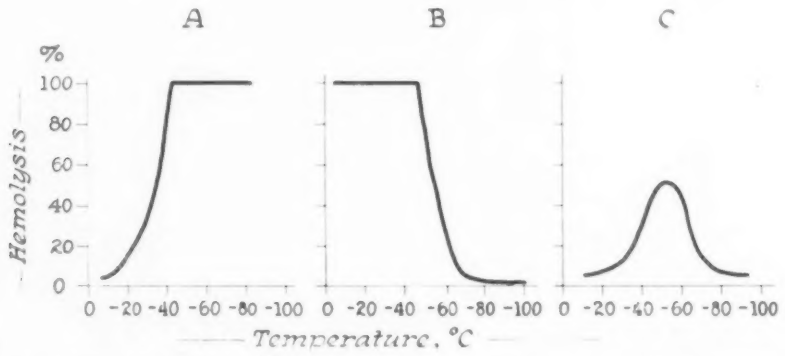

Fig. 4.—*A*. Theoretical curve showing relationship of temperature to hemolysis, assuming that only a "salt-effect" is operative. *B*. Same, assuming that only a "mechanical effect" by ice crystals is operative. *C*. Curve obtained experimentally[8].

The second theory also finds support from: (a) the fact that materials which prevent hemolysis at —79° C. strongly hydrogen bond and therefore distort the ice lattice; (b) data showing that high molecular weight polyoxy compounds prevent hemolysis due to freezing at —79° C. although these compounds do not enter the erythrocytes. This theory also predicts that there should be a sharp increase in hemolysis as the temperature goes from —60° to —45° C. and that from about —45°

to 0° C. there should be 100% hemolysis. This theory is illustrated in Fig. 4B.

The curve of hemolysis versus temperature obtained by experiment[8] exhibits a maximum in the region —45° C. to —55° C. as is shown in Fig. 4C. When temperatures from —50° C. to —192° C. are used the range from 0° C. to —40° C. is passed rapidly and the salt effect is small compared to the effect of mechanical disruption of the cell by ice crystals. However, from 0° C. to —40° C. the effect of the ice crystals is small compared to the effect of the salt. It is therefore suggested that both mechanisms are operative, with damage of the cells due to high salt concentration predominating from 0° C. to —50° C. and disruption of the cells due to ice crystals predominating at lower temperatures.

Summary. It is concluded that:

1. "Pluronic" F-68 and "Tetronic" 707 in a concentration of 25% and "Polyglycol" E-6,000 and E-9,000 in a concentration of 20% protect 94% of a suspension of human erythrocytes from hemolysis due to rapid freezing and thawing.

2. Agglutination *per se* does not protect the cells from hemolysis due to freezing and thawing.

In addition the following hypotheses are proposed:

1. Compounds which protect the human erythrocytes from hemolysis due to freezing and thawing should have a polar carbon to oxygen bond and should also have the oxygen available for bonding to the hydrogen of water.

2. These compounds need not enter the erythrocyte in order to be fully effective in preventing hemolysis.

3. The mass *per se* of the polymer does not protect the cells from hemolysis due to freezing and thawing.

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(Interlingua on page 74)

A PRELIMINARY STUDY OF SMALL BOWEL MUCOPROTEINS IN TROPICAL SPRUE

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and

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The absorption defect in tropical sprue is ill defined. At the present time the nutritional deficiency of folic acid or Vitamin B_{12}, or both, has been the predominant explanation for the disease in the Caribbean Area[3]. However, past experiences in Puerto Rico and India have suggested that some patients continue to have minimal or intermittent symptoms despite a hematologic remission. A previous report of Smart and Daley[4] suggested that the mucous secretions of the small bowel may be abnormal in sprue and interfere with fat absorption. Also *in vitro* studies have demonstrated flocculation of barium suspensions by mucous materials[1]. Such observations have suggested that the mucous secretion in the small bowel may be increased or altered in function. The present study was initiated to determine if any changes could be observed in the small bowel mucoproteins that might aid in the elucidation of the absorption defect of fats and sugars.

Methods and Material. Three groups of patients were studied. Seven patients with untreated tropical sprue, 6 treated tropical sprue patients and 11 patients with sprue syndrome. Patients with tropical sprue were diagnosed by the criteria of weight loss, diarrhea and lassitude, associated with macrocytic anemia and a megaloblastic bone marrow. Such patients also had impaired absorption of sugars and fats. The term treated tropical sprue designates patients who have been receiving oral folic acid daily for at least 3 months (5 of the 6 studied had received therapy for more than one year). These patients had the criteria for the diagnosis of tropical sprue before receiving treatment. The term Sprue Syndrome has been used to separate a group of military personnel who had had the signs and symptoms of intestinal malabsorption but have not had macrocytic anemia. Their disease is moderately acute and has been reversible when treated with oral folic acid. These patients were studied before treatment with folic acid.

Fifteen volunteer control patients were studied. They were selected as individuals free of gastrointestinal symptoms that could suggest tropical sprue or intestinal malabsorption. Although their history and laboratory studies suggested no diagnosis of sprue, specific intestinal absorption and small bowel roentgenographic studies were not done in this group.

A double lumen intestinal tube was used for intubation. A rubber bag containing 3 ml. of mercury was tied to the end of the tube to aid in passing the tube into the duodenum. The tube was passed into the stomach and the initial gastric contents were collected and discarded to eliminate saliva contamination. A sample of gastric juice was collected for analysis and immediately placed in an ice chilled flask. The patient was then positioned on his right side to facilitate passage of the tube into the duodenum. Progress of the tube was observed by fluoroscopy. The tube was allowed to pass to a distance estimated to be 20 cm. beyond the ligament of Treitz. This distance may be considered only an approximation, for it is understood that "telescoping" effect may indicate a greater distance than estimation or measurement on the fluoroscopic screen. Usually 2 hours were required to locate the tube for sampling. About one-half

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of the attempted intubations were successful.

Small bowel juice was collected by aspiration and immediately placed in an ice chilled flask. Usually 30 to 45 minutes were necessary to collect 20 to 30 ml. of juice. There appeared to be no free secretion in the jejunal section but rather one felt that the presence of the rubber tube may have acted as a stimulant or irritant to promote the secretion of a few drops of juice irregularly. All samples were bile stained.

The chilled gastric and small bowel juices were taken to the laboratory and the method of Glass and Boyd[2] used to separate chemically dissolved mucoproteose and mucoprotein fractions. Final values are expressed as milligrams of protein per 100 ml. of gastric or small bowel juice. The protein content is measured by comparison with a tyrosine standard. The tyrosine equivalents for gastric juice have been used to calculate small bowel fractions. The tyrosine content of dissolved mucoprotein was 7.2 mg. per 100 ml. of dry weight. These values are within the range of results listed by Glass and Boyd for dissolved mucoprotein of gastric juice. Such a similar tyrosine content does suggest that the gastric juice method may be applied to fractionation of small bowel juice.

Results. 1. GASTRIC JUICE. The initial centrifuged juice revealed no volume changes in the various groups of patients to indicate percentage differences in visible mucus. The samples of fasting juice were fractionated into dissolved mucoproteose and mucoprotein. The results are tabulated in Table 1. No significant differences exist in these groups. The groups of patients are small but the mean values are similar to the ranges listed by Glass and Boyd. All patients studied except one in the treated sprue group had free gastric acid. Gastric juice was not titrated in units, but only examined for presence or absence of free acid.

2. SMALL BOWEL JUICE. The tabulated values for the dissolved mucoproteose and mucoprotein fractions are listed in Table 1. There is some noticeable difference in the dissolved mucoprotein fraction. These individual values are therefore plotted in Fig. 1 for comparison.

Discussion. The small number of observations in this study would indicate that no significant changes could be demonstrated in the gastric dissolved mucoproteose and mucoprotein values. The gastric mucoprotein values may be somewhat increased because of the collection procedure. Glass and Boyd have indicated that the presence of the rubber tubing may stimulate the parietal cells and increase the dissolved mucoprotein content in the gastric juice. Hence the values obtained in all patients undoubtedly show variation associated with such stimulus. Because fluoroscopic facilities were limited, it was not feasible to use a double balloon tube to limit the segment of small bowel in which juice was collected. The possibility of gastric juice contamination cannot be excluded. However a comparison of gastric and small

TABLE 1.—DISSOLVED MUCOPROTEOSE AND MUCOPROTEIN FINDINGS IN GASTRIC AND SMALL BOWEL JUICE FROM 39 SUBJECTS

	*Controls (15)**	*Sprue Syndrome (11)**	*Untreated Sprue (7)**	*Treated Sprue (6)**
Dissolved gastric mucoproteose	60 (48)	48 (48)	75 (42)	82 (62)
Dissolved gastric mucoprotein	28 (13)	13 (9)	27 (16)	27 (21)
Dissolved small bowel mucoproteose	144 (60)	116 (60)	122 (30)	120 (54)
Dissolved small bowel mucoprotein	33 (18)	10 (13)	14 (10)	4.4 (5)

* Number of patients studied in each group.

Mean values for each fraction are listed and one standard deviation is designated in parenthesis. Values refer to milligrams per 100 ml. of gastric or small bowel juice as defined by a tyrosine standard.

bowel dissolved mucoprotein was made and no correlation could be found.

It is recognized that the application of the gastric juice separation technique to the small bowel juice may be criticized. Little information is available concerning mucoproteins of the succus entericus. The present chemical separation at best is a crude analysis. It was not possible at this time to define carefully these fractions of the small bowel. It is hoped that these suggestive preliminary observations may stimulate further investigations of the small bowel secretion.

If these values can be accepted there are changes in the dissolved mucoprotein values of the small bowel juice. In the military patients, that have been designated by the sprue syndrome group, the values are low; but there is some variation in the results. It is recognized that the disorder is seen with varying degrees of duration and malabsorption as indicated by variation in specific absorption tests. Hence one may expect to observe differences in the values obtained. Only limited observations were made in the untreated sprue group. These patients were ill and had marked anemia, and only a small number could be selected safely to tolerate the procedure. Probably the treated sprue patient reflects the more chronic defect of the small bowel secretion. A review of the ab-

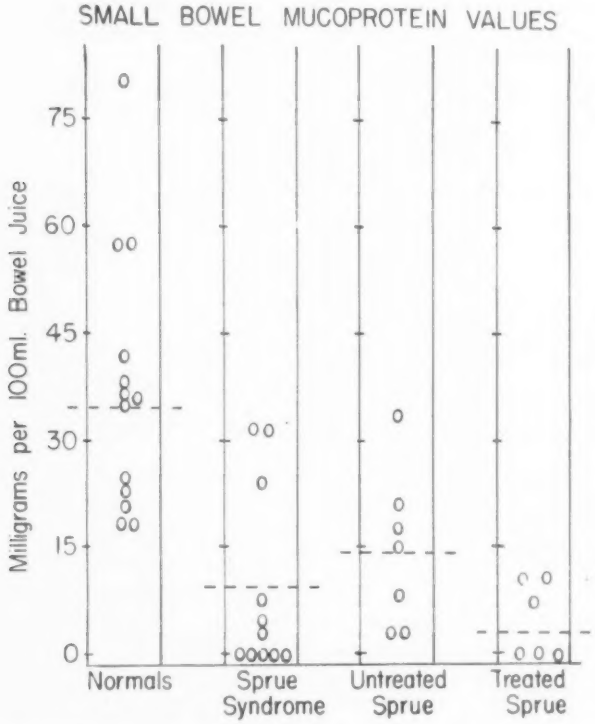

Fig. 1.—Tabulated values for dissolved mucoprotein of the small bowel juice. The dotted lines across each bar indicate the mean values of the group observations.

sorption tests would indicate that these patients maintain a continuous absorption defect despite hematological improvement. The mucoprotein abnormalities of the small bowel then would persist and the defect would be accentuated with prolongation of the disease.

Despite the radiologic evidence of segmentation of the barium meal and hypersecretion, the sprue patients in this study did not have increased fluid mucus by aspiration in the small bowel lumen when compared with normal subjects. Although *in vitro* studies have demonstrated clumping of barium by mucus, such phenomena must be associated with the mucus barrier adherent to the intestinal epithelium rather than to excess secretion.

These observations are preliminary but may contribute to further understanding of the nutritional defect in tropical sprue. The alterations in the content or amount of dissolved mucoprotein may indicate changes in the mucus surface that impairs proper absorption of foodstuffs.

Summary. Samples of gastric juice and small bowel juice collected from the jejunum were analyzed chemically for dissolved mucoproteose and mucoprotein by the method of Glass and Boyd. Although the number of patients studied was small, suggestive changes in the small bowel values of dissolved mucoprotein were observed in the sprue patients. These alterations may be associated with the intestinal malabsorption of foodstuffs and reflect metabolic abnormalities of the intestinal epithelium.

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SUMMARIO IN INTERLINGUA

Un Studio Preliminari del Mucoproteinas del Intestino Tenue in Sprue Tropic

Specimens de succo gastric e de succo del intestino tenue colligite ab le jejuno esseva analysate chimicamente pro dissolvite mucoproteosa e mucoproteina per le methodo de Glass e Boyd. Ben que le numero del patientes studiate non esseva extense, nos crede poter attribuer un fortia suggestive al alterationes observate in patientes de sprue in le valores de dissolvite mucoproteina in le intestino tenue. Iste alterationes pote esser associate con defective absorption intestinal de alimentos e reflecte anormalitates metabolic in le epithelio intestinal.

A CLINICAL EVALUATION OF THE USE OF A RECTAL MERCURIAL DIURETIC IN PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE

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In spite of the progress of the past few years in mercurial diuretic therapy, the problem of self-administration remains. Development of a preparation that can be given subcutaneously and used by the patient at home was a significant advance. Similarly, oral preparations have found their place in the physician's armamentarium. There are patients, however, in whom neither of these has been entirely satisfactory due to inconvenience or side reactions.

Recently mercaptomerin sodium (Thiomerin) was made available in suppository form†. Early clinical trials with this dosage form were encouraging, the preparation appears effective and notably free from side effects[1]. Further clinical evaluation seemed warranted. It was our purpose to evaluate the usefulness of these suppositories in patients with chronic congestive failure and to determine whether they could be used for long periods without irritation or toxicity.

Method. Twenty-three patients suffering from heart disease of arteriosclerotic (9), hypertensive (5), rheumatic (4), luetic (3), congenital (atrial septal defect) (1), and unknown (1) type were selected from a large group attending the Cardiac Clinic of the Pennsylvania Hospital. All were considered to be in chronic congestive heart failure, were digitalized and had been receiving parenteral mercurial diuretics for at least 3 months prior to the study.

Accurate records of all injections given were available for the control period. Most had received at least one injection a week and several were receiving two or more. Excluded were patients who were uncoöperative or in whom the need of mercury was not readily confirmed. None were eliminated because of intolerance to suppository medication. A placebo period was included for 7 patients who apparently responded well to the mercurial suppositories. In five instances, a "double blind" method was used in which the physician treating the patient did not

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†Thiomerin (mercaptomerin) suppositories were supplied through the courtesy of Wyeth Laboratories. Each suppository contains 0.5 gm. of mercaptomerin sodium (equivalent to 165 mg. of mercury) in a cocoa butter base.

know whether or not the suppositories contained mercury.

Complete blood count, urinalysis, blood urea nitrogen, serum chloride and creatinine were obtained, and proctoscopy was performed. On completion of these studies, therapy with suppositories was started. All patients were given one suppository daily and if there was no apparent response the dose was doubled. The amount of additional parenteral mercury needed was carefully recorded. Placebo suppositories were then substituted in all patients whose need of parenteral therapy had been greatly reduced. This was continued for at least 3 months or until cardiac failure ensued. Placebo medication was not used in those who required supplementary parenteral therapy during treatment with suppositories. After cessation of suppository therapy the parenteral mercurial requirement was again carefully recorded. Two patients who had done especially well on the suppositories were restarted, following the placebo period, for long-term evaluation. One received therapy for 12 and another for 15 months without evidence of irritation or toxicity. As far as possible, additional therapeutic measures and other factors in the clinical management were kept constant; namely, digitalis, ammonium chloride, low salt diet, and the like.

Results. The effectiveness of suppository therapy was determined by the clinical findings and by comparison with the number of weekly mercurial injections required before, during and after use of the suppository.

The mean parenteral mercurial requirement for the 23 patients, during an average 27.2 week control period, was 1.1 injections per week. (Table 1 and Fig. 1). During the latter half (13.6 weeks just prior to suppository therapy) the mean number of injections received was 1.2 per week. On an average of 7.3 suppositories per week, the mean number of parenteral mercurial injections fell to 0.5 per week during an average of 13.6 weeks. This decrease of 0.7 injections during the comparable time periods is likely to occur by chance in less than one time per thousand ($p = <0.001$). During the average 14.8 weeks following the use of the suppositories the number of mercurial injections rose to 1.2 per week.

Seven of the 23 patients required a mean of 1.1 injections per week during the average 27.2 week control period, as did the entire group of 23, although during the latter 13.6 weeks only 1.0 weekly injection was received as compared to the 1.2 per week for the entire group (Tables 1 and 2). During an average of 17.2 weeks on an average of 6.9 suppositories per week, the parenteral mercurial requirement fell to zero, and continued at that level on substitution of placebo suppositories for an average of 15.9 weeks. After another 15.4 weeks on no suppository medication, the mercurial requirement rose to 0.4 injection per week.

The 16 remaining patients whose parenteral mercurial need persisted during suppository therapy or returned immediately after its cessation had mercurial requirements similar to those of the entire 23 patients for the control period (Tables 1 and 3). During an average of 12.4 weeks on an average of 7.5 suppositories per week, the number of injections fell from a mean of 1.2 per week during the 13.6 weeks immediately preceding to a mean of 0.8 injections per week. This reduction of 0.4 injections per week could be expected to occur by chance less than one time in one hundred ($p = <0.01$). On cessation of suppository therapy the number of injections rose to a mean of 1.8 per week in the 14 remaining patients that could be followed. Two patients were hospitalized for reasons other than congestive failure and could not be followed as outpatients.

It was found that an average of 6.8 suppositories a week reduced the number of parenteral mercurial injections by a mean of 0.4 per week or 68.6% in 7 patients found to require less than 1.0 injection a week. In those patients

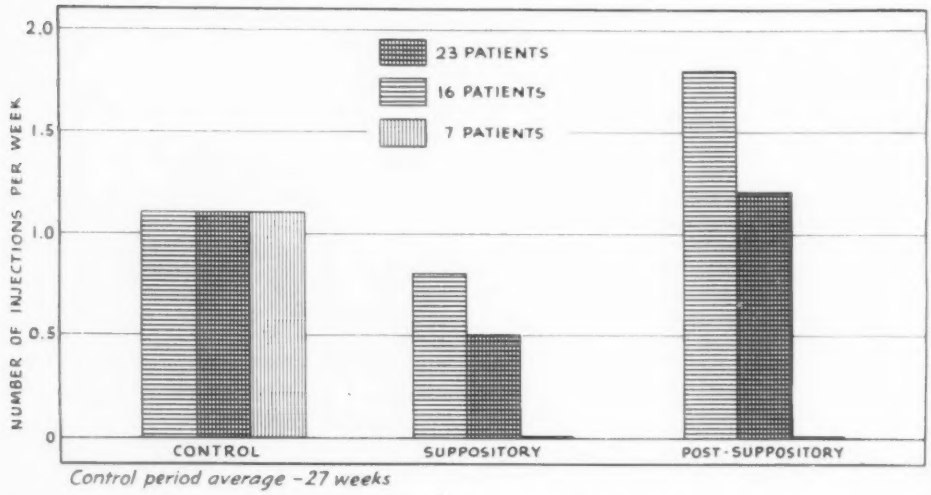

Fig. 1.—The number of weekly mercurial injections required by 23 patients in congestive heart failure before, during and after suppository therapy.

TABLE 1.—THE EFFECT OF MERCURIAL SUPPOSITORIES ON PARENTERAL MERCURIAL REQUIREMENTS OF 23 PATIENTS WITH CONGESTIVE HEART FAILURE

	Control Period			*Suppository Period*	*Post-suppository Period*
	First Half	*Second Half*	*Total*		
Number of patients	23	23	23	23	21
Weeks: Average	13.6	13.6	27.2	13.6	14.8
Range	–	–	12.7–58.0	5–26	1–41
Injections: Number per week	1.0	1.2	1.1	0.5	1.2
Standard deviation	±0.44	±0.58	±0.47	±0.91	±1.45
Suppositories: Number per week	0	0	0	7.3	0
Range	0	0	0	3.8–14.0	0

TABLE 2.—THE EFFECT OF MERCURIAL SUPPOSITORIES AMONG 7 PATIENTS WITH A DECREASING NEED FOR MERCURIAL DIURESIS

	Control Period			*Suppository Period*	*Placebo Suppository Period*	*Post-placebo Period*
	First Half	*Second Half*	*Total*			
Number of patients	7	7	7	7	7	3
Weeks: Average	13.6	13.6	27.2	17.2	15.9	15.4
Range	–	–	15–58	12–26	11.5–26.0	9.1–20.0
Injections: Number per week	1.2	1.0	1.1	0	0	0.4
Standard deviation	±0.45	±0.54	±0.5	0	0	0.45
Suppositories: Number per week	0	0	0	6.9	Placebos	0
Range	0	0	0	6.5–7.0	..	0

requiring 1.0 to 1.9 injections a week, an average of 7.5 suppositories per week reduced the number of weekly injections by 0.6 or 49.6%. In those needing from 2.0 to 2.9 injections a week (3 patients) an average of 7.1 suppositories per week reduced the mean number of injections by 1.3 per week or 57.7%. Thus in the entire 23 patients, an average of 7.3 suppositories per week reduced the number of injections by a mean of 0.7 per week or 54.0%.

In 13 of the 16 patients with established need of a mercurial diuretic a significant reduction was demonstrated in the amount of parenteral mercury required. In 7 of these 13, the need of supplementary injections was reduced to less than one per month but during the placebo period returned to the previous requirement. Thus of the entire 23 patients, 9 needed no parenteral mercury at all during suppository therapy and in 14 the injections were reduced to less than one per month.

Due to the severity, chronicity and progression of their disease, the clinical evaluation of these patients was difficult. Only in those patients in whom the need of parenteral mercury was greatly reduced was this result clinically appreciated by the physician following the patient. No significant trend in weight was noted, since they had received treatment with mercurial diuretics for a period prior to the suppository study. Doubling the dose of suppositories in the patients with severe failure who had failed to respond significantly was of little benefit.

Three patients died during the course of this study. One, suffering from luetic and arteriosclerotic heart disease, had carcinoma of the esophagus, proved by necropsy. The other two, believed to have arteriosclerotic heart disease, died unexpectedly with terminal episodes of suspected acute myocardial infarction. In one of these congestive heart failure increased on reduced amounts of mercurial diuretics. Carcinoma of the stomach developed in a fourth patient with arteriosclerotic heart disease, who required no parenteral therapy during treatment with mercurial suppositories or placebos, making final evaluation difficult.

SIDE EFFECTS AND TOXICITY. One patient developed a rash which a dermatological consultant thought was a dermatitis medicamentosa. Besides mercurial therapy she was receiving aminophylline, digitalis and ammonium chloride. This rash improved despite continued parenteral mercurial therapy. This patient had arteriosclerotic heart disease and long-standing diabetes mellitus, renal disease, a rising blood urea nitrogen and increasing anemia.

Laboratory studies were rechecked after 1 to 7 months (3 months average) of suppository therapy. Seventeen patients had complete blood counts. In only one was there a drop in the red blood cell count. For only one of the 16 patients was any change in the urinalysis observed; an increased number of casts and red blood cells appeared in the urine. This patient had hypertensive cardiovascular disease with a large aneurysm of the descending thoracic aorta that had enlarged rather markedly during the year of study.

In 17 patients the blood urea nitrogen, and in 15 patients the creatinine determinations, were repeated. Two had a rise in blood urea nitrogen, one with increasing congestive failure and one with renal disease. One patient who had a slightly elevated blood urea nitrogen and creatinine had no pretreatment control values. Significant elevation in the serum creatinine did not occur in any of the patients. Serum chloride determinations were done after 1 to 7 months (3 months average)

of therapy. The only significant change was a fall of about 10 mg. in the 2 patients with carcinoma. In one, weight loss and dehydration accompanied the chloride fall. In the absence of vomiting this effect was attributed to the mercurial suppository therapy.

Proctoscopic examinations, repeated in 13 patients after 2 to 15 months (average 4 months) of therapy, revealed no significant change. Rectal strictures did not prevent use of the suppositories and hemorrhoids were not aggravated. In two instances anal and perianal inflammations disappeared. Two patients complained of rectal burning with both the placebos and the mercurial suppositories. One patient experienced burning only with the placebo.

COMMENT. Evaluation of the effectiveness of mercurial diuretics in patients with chronic congestive failure is difficult because of the lack of reliable objective criteria for comparison. Comparing the urinary output from an oral or rectal preparation with that from a parenteral preparation tends to be inaccurate as well as misleading in outpatient studies. It is well known that intermittent injections result in weight and urinary output fluctuations, whereas more regular administration of nonparenteral preparations seem to maintain a more stable fluid balance. Many patients, when first started on mercurial suppositories, missed the usual large postinjection diuresis. Weight fluctuations were greatly reduced or eliminated, resulting in better maintenance of the patient's functional capacity and well-being. The usual method of weight comparison was found inadequate since patients' weight often varied as much as 5 pounds with no apparent change in therapy. Since this was an outpatient study, seasonal variation in clothing may have been a factor. Even though the patients were instructed in the principles of dietary restriction, it is doubtful if many adhered closely. Variations in salt intake might thus account for some of the weight fluctuations. In addition, spontaneous improvement in congestive failure may be a factor and give a false impression of the effectiveness of the preparation being investigated. Evidence to support this may be seen in the 7 patients whose mercurial requirements disappeared during the study. During the initial control period the need of mercury in these patients was decreasing as compared to the increasing requirement of the other patients (Table 2).

In contrast the 16 patients, in whom the need of mercury was established, showed an apparent progression of failure as manifested by an increased requirement for mercury during the entire period of study (Table 3). The parenteral diuretic requirement of the post-suppository control period was actually underestimated, since 6 of these patients on placebos showed a slowly progressive failure and received fewer injections than optimal. It was also noted that many patients displayed a psychological dependence on their "shots" which may have influenced the attending physician. This probably produced an unduly high mercurial requirement during the initial control period of some patients. We attempted to control this variable by use of placebos in both parenteral and suppository form. The inherent difficulties in evaluating a diuretic in patients with chronic congestive failure can best be minimized by long periods of observation and by use of placebos. Several patients received placebo suppositories for more than 3 months before symptoms and signs of congestive failure reappeared. Determination of parenteral mercurial requirements during a

long observation period would seem to be the best single measurement of therapeutic efficacy.

Summary. In a study of 23 patients who required one or more injections of a mercurial diuretic per week during a control period, an average of approximately one suppository a day reduced the parenteral mercurial requirement by more than half. Nineteen of the 23 required less than one injection weekly during suppository therapy; 14 required less than one monthly, and 9 required no parenteral mercury.

In contrast to mersalyl (Salyrgan) and mercuzan[2] (Mercurin), and similar to meralluride[2] (Mercuhydrin), the suppository form of mercaptomerin (Thiomerin) appears to have no local toxic or irritative effects. In this study none of the patients showed either subjective or objective evidence of rectal irritation, in spite of prolonged use.

Mercaptomerin (Thiomerin) suppositories are effective in reducing or eliminating the need for parenteral mercury in many patients with chronic congestive heart failure.

TABLE 3.—THE EFFECT OF MERCURIAL SUPPOSITORIES AMONG 16 PATIENTS WITH AN INCREASING NEED FOR MERCURIAL DIURESIS

	Control Period			*Suppository Period*	*Post-suppository Period*
	First Half	*Second Half*	*Total*		
Number of patients	16	16	16	16	14
Weeks: Average	13.6	13.6	27.2	12.4	11.0
Range	–	–	12.7–42.0	5–19	1–41
Injections: Number per week	0.9	1.2	1.1	0.8	1.8
Standard deviation	±0.44	±0.57	±0.46	±1.00	±1.56
Suppositories: Number per week	0	0	0	7.5	0
Range	0	0	0	3.8–14.0	0

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SUMMARIO IN INTERLINGUA

Un Evalutation Clinic del Uso de un Rectal Diuretico Mercurial in Patientes con Chronic Disfallimento Congestive del Corde

In un studio de 23 patientes, qui habeva requirite durante un periodo de controlo un o plure injectiones de diuretico mercurial per septimana, il esseva constatate que le uso median de circa un suppositorio per die reduceva le requirimento parenteral del diuretico mercurial per plus que 50 pro cento. Durante le therapia a suppositorios, 19 del 23 requireva minus que un injection per septimana; 14 requireva minus que un injection per mense; e 9 requireva nulle injection del toto.

In contrasto con mersalyl (Salyrgano) e mercuzano (Mercurino), e simile a meralluride (Mercuhydrino), le forma suppositorial de mercaptomerino (Thiomerino) ha apparentemente nulle local effecto toxic o irritative. In le presente studio, nulle del patientes monstrava objective o subjective signos de irritation rectal, in despecto de un curso prolongate.

Suppositorios a mercaptomerino (Thiomerino) es un medio efficace pro reducer o eliminar le requirimento de mercurio parenteral in multe casos de chronic disfallimento congestive del corde.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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THE SPRUE SYNDROME

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ALTHOUGH early descriptions of the sprue syndrome are few in number, its antiquity is established. Haas and Haas[93] discussed interestingly the history of celiac disease of which the first clear account was given by Aretaeus of Cappadocia[15] in the second century, A.D. Caelius Aurelianus of Numidia[17] wrote of the condition, probably in the fifth century, A.D., and perhaps based his description upon the views of Soranus, a Greek physician of the second century, whose writings Aurelianus translated into Latin. The following twelve centuries, however, do not appear to be well represented in extant descriptions. Garrod and Hurtley[85] stated that Tulpius[212] described the condition in the seventeenth century and that the term 'steatorrhea' was first used in 1824 by Kunzmann[127]. Bright[32] and Gull[91] published clinical descriptions but Samuel Gee's[86] short paper "On the Coeliac Affection" published in 1888, is regarded as marking the beginning of present-day interest; this paper, 'a classic clinical cameo'[160], is a model of accuracy in observation.

Herter[102], in New York, described celiac disease in 5 children under the title "Infantilism from Chronic Intestinal Infection," and, although he stressed the probability of infection as the causative factor, he noted the intolerance to carbohydrates and fat in the diet, as did Heubner[103] in Germany. Heubner described what he termed 'intestinal insufficiency' in 10 children.

The word 'sprouw' was first used by the Dutch physician, Ketelaer[125], when he described in 1699 the condition of aphthous stomatitis in association with 'a most pernicious diarrhoea.' Hillary[106] described the same condition in the

Barbadoes but the term 'sprue' was first applied to the disease by van der Burg[35] in Java and by Manson[139] in China, each in the year 1880.

Tropical sprue was recognized in patients returning to the United States[104] and also among those who had never been abroad[226]. Holst[108] described a case of sprue in Denmark and used the term 'non-tropical' sprue. Thaysen[206] held that the recognition of nontropical sprue formed the connection between Gee-Herter's disease (celiac disease) and tropical sprue. He considered that these three conditions were related to, if not identical with, one another and collected them together as 'idiopathic steatorrhoea.' Gee[86] had stated that celiac disease occurred most often in children between one and five years old but noted that it was seen in Englishmen returning from India and also, although seldom, in adults who had never left the island.

The sprue syndrome comprises these three conditions, tropical sprue, nontropical sprue in the adult and celiac disease in the child[59,76,78,95,112]. Many authors[95,97,112,154,207,208] have maintained that there is no fundamental difference between the three conditions, whereas others[24,25] consider it possible to identify the particular disease entity. To Manson-Bahr[141] the conditions are 'outwardly similar but inwardly dissimilar.' Clinical features in common and lack of precise knowledge of pathogenesis appear to warrant the juxtaposition, but there are distinctive characteristics and it is probable that the same clinical syndrome may be produced in different ways.

Celiac disease essentially affects children although it may not be recognized until adolescence and the symptoms have been found to persist into adult life[25,87,98,172,228]. Gerrard and associates[87] re-examined 32 patients whose ages ranged from 4 to 19 years and in whom a diagnosis of celiac disease had been made in early childhood. All had been maintained on diets containing wheat gluten and in none was recovery complete. Moreover, many adult patients with nontropical sprue have been found to have had celiac disease or to have had symptoms compatible with celiac disease in childhood[25,53].

The anemia of celiac disease is commonly microcytic, whereas in both nontropical and tropical sprue macrocytic anemia is more common. Of the other complications of celiac disease, dwarfism, infantilism and rickets are more to be regarded as being related to the age of onset and to the severity of the disease than as characteristic points of differentiation from the adult disease. Celiac disease responds well to elimination of wheat gluten from the diet, even when this measure is adopted late in the illness[88]; of adults with nontropical sprue, however, only a few have responded satisfactorily[13].

In tropical sprue epidemic outbreaks may occur[195,215], often times several members of the same family, but rarely children, being affected ('sprue houses')[21]. The anemia is usually macrocytic, sore tongue is very frequent and, despite the possibility that relapse may occur, a rapid recovery in most cases may be expected to follow the institution of therapy[122]. In many instances it is often very difficult to distinguish between tropical sprue and tropical macrocytic anemia, and between sprue and the effects of severe malnutrition.

During the last decade much has been learned of the incidence of the sprue syndrome and of its occurrence in latent form, diagnostic criteria have become more uniformly accepted, new methods of treatment have been successfully adopted and some clarification

of ideas upon the pathogenesis of this interesting condition has been achieved. It is the purpose of this review to consider more fully these aspects of the sprue syndrome.

INCIDENCE. Twenty years ago celiac disease and nontropical sprue were regarded as relatively uncommon conditions[174]. It appears now, however, that the incidence is greater than was formerly suspected, partly because of greater awareness of the existence of the disease, because of activity by clinical research workers, and partly because of the recognition of mild and latent forms of sprue. Haas and Haas[93] studied 603 cases of celiac disease in New York. Thompson[210], who studied 119 cases in Ontario, stated that Ebbs had estimated the incidence of celiac disease in children in Toronto to be between 1 per 100 and 1 per 1000. Cooke and associates[53] described 100 cases of nontropical sprue in Birmingham, England, and Davidson and Fountain[59], making use of the existence of food rationing in Britain in estimating the incidence of the sprue syndrome, found that the total number of patients with sprue applying for extra food rations between January, 1943, and December, 1948, was 2044, of whom 1303 had celiac disease, 311 nontropical sprue, 403 tropical sprue and the remaining 27 were unclassified because of insufficient information.

The incidence of tropical sprue is more difficult to estimate. Of 8846 medical patients in the army returned to Britain as invalids between February, 1943, and February, 1946, 1073 had tropical sprue[121]. Stefanini[195] studied 1069 cases of tropical sprue occurring in Italian prisoners-of-war in India. Among recent publications are those of Rodriguez-Molina[167], who studied 100 cases of tropical sprue in Puerto Rico, and of Lopez and associates[132], who studied 155 cases in Cuba.

A great deal of interest has been aroused by the occurrence of the sprue syndrome in members of the same family. Thompson[210] recorded instances of familial occurrence reported in the literature and among her own patients, and concluded that the incidence of celiac disease in siblings was far greater than would be expected through chance alone. Increasing maternal age and lateness of birth rank appeared to be predisposing factors. In their survey, Davidson and Fountain[59] found a sufficient number of familial cases to suggest the possibility of there being a genetic factor of etiological importance. Andersen and di Sant'Agnese[9] found 6 siblings with celiac disease in their study of 58 cases. An interesting finding is the tendency for diabetes mellitus to occur in the families of children suffering from celiac disease[9,65]. There are the 'sprue houses' of tropical sprue[21], and the findings of Suarez[198] are very striking. In a study of 150 patients suffering from tropical sprue in Puerto Rico, Suarez obtained a reliable history of sprue or of pernicious anemia in the patients' parents, usually the mothers, in 75%.

LATENT SPRUE. The nondiarrheal phases of celiac disease and the interval of relative freedom from symptoms occurring between celiac disease in childhood and the appearance of nontropical sprue in the adult have been termed 'latent coeliac disease'[25,53]. When the feces are examined during these latent phases, excessive quantities of fat are still found[87,172]. The interval of freedom from symptoms between an initial attack of tropical sprue and its recrudescence, often many years later and with the patient no longer living in the tropics, has been described as one of 'latent sprue'[140]. Another form of latency which has gained increasing recognition in recent years occurs in patients who first pre-

sent themselves with complications of the sprue syndrome and in whom there is little or no initial evidence of the underlying intestinal absorptive defect[10,25,36,53,58,100,114,161,197]. The presenting features may be mild ill-health, diarrhea, glossitis, bone-pain, tetany, rickets, osteomalacia, the Looser-Milkman syndrome, iron deficiency anemia and megaloblastic anemia. These features may occur singly or in conjunction and their significance may not be appreciated for several years. Cooke and his associates[53] found among their cases of the sprue syndrome many instances of chronic diarrhea which had previously been labelled mucous colitis, lienteric diarrhea, 'colitis' and nervous diarrhea. Megaloblastic anemia, occurring particularly in young subjects and often refractory to potent parenteral liver extracts[49,53,114], and iron deficiency anemia that fails to respond to oral iron therapy[100], merit further investigation.

DIAGNOSIS. Andersen and di Sant'-Agnese[9] considered that no single test was pathognomonic of celiac disease and that the diagnosis should be based upon the clinical and laboratory picture as a whole rather than upon the presence or absence of single factors. In their cases the diagnosis was first suspected on clinical grounds in patients showing the 'celiac triad' of persistent diarrhea, loss of weight and an enlarged abdomen. Laboratory techniques were then applied to exclude other conditions in which this clinical picture occurs and to confirm the diagnosis of celiac disease. Finally, they regarded a satisfactory response to a therapeutic dietary regimen as providing important confirmation. This very rational approach to diagnosis is applicable to the sprue syndrome as a whole and predicates a clinical awareness of the manner in which the disease is manifested and of the guises under which it may masquerade.

The symptoms and signs of celiac disease have been well described by Haas and Haas[93] and by Parsons[160], of nontropical sprue by Cooke and associates[53] and of tropical sprue by Manson-Bahr[142] and others[121,123,167,195]. Anderson and di Sant'Agnese[9] drew attention to differences between the clinical features of celiac disease as seen today and those of the classical descriptions. For example, celiac disease appears now to have its onset at an earlier age than formerly whereas celiac disease with rickets, once common, is now rarely seen. The authors attribute these differences to the current practice of artificial feeding of babies and the use of vitamin supplements.

Demonstration of defective fat absorption is the most useful procedure in the diagnosis of the sprue syndrome. Steatorrhea in its overt form, as in the graphic descriptions of Aretaeus and Gee, is not difficult to recognize. However, feces with a high fat content may appear grossly normal[29,153], and when the dietary fat is low there may be no apparent steatorrhea[23]. Sometimes patients may themselves learn to avoid eating fat. Fat absorption has been studied by determination of plasma lipid levels and by determination of fecal fat excretion.

Plasma Lipid Levels, Fat and Vitamin A Absorption Tests. In celiac disease the fasting levels of total fatty acid in the plasma have been described as lower than normal[69,159], within normal limits[69,136] and above normal[156]. In sprue total fatty acid at normal or above normal levels[5,30] and phospholipid and cholesterol below normal levels[30,69] have been described. After a fat-containing meal the rise in plasma fatty acid levels has been found less than normal in celiac disease[69,159] and in sprue[5,22,30]. By the technique of counting chylomicrons in the blood[67,81,82], Cooke and associates[51] observed a low degree of lipemia following a fat

meal in the sprue syndrome. Fourman[72], however, found little relationship between the height of the chylomicron curve and the quantity of fat excreted in the feces in sprue.

Absorption of vitamin A given orally in oil has been widely employed as an index of fat absorption. Low plasma vitamin A levels and flat absorption curves have been found in celiac disease[4,31,44,144,145,146] and in sprue[5,41,57,113,129,162]. Andersen and di Sant'Agnese[9] did not consider the vitamin A absorption test useful in the diagnosis of celiac disease but confirmed the finding of low plasma carotene levels[9,44,144,145]. Legerton and associates[129] and Paterson and Wiggins[162] considered the vitamin A absorption test a valuable screening procedure in that adequate absorption of vitamin A appeared to exclude steatorrhea. Curves of lipemia and of plasma vitamin A following test meals, however, reflect the rate of absorption rather than the quantity absorbed.

Fecal Fat Excretion. Microscopic examination of the feces and chemical determination of the fat content of single fecal samples do not yield adequate diagnostic information[27,51,219]. Since steatorrhea may be minimal when the fat content of the diet is low, it is necessary to ensure adequate and constant fat intake, and the collection of cumulative samples of feces is advised in order to minimize the error in daily collections. Fourman and associates[73], using diets containing 70 gm. fat daily and 4-day collection periods, found a mean excretion of 11.54 ± 3.83 gm. over the period of 4 days in normal subjects. The probable upper limit of normal for 4-day fat excretion (mean + 3 × S.D.) was estimated to be 23 gm. For three consecutive 4-day periods the probable upper limit of normal (12-day mean + 3 × S.D.) was found to be 54.2 gm. These authors recommended the use of a 12-day period when the effects of therapy were being studied. Wollaeger and his associates[223,224] fed diets containing 101.6 gm. fat and 208 gm. fat to normal individuals and obtained a mean daily fat excretion of 4.1 ± 0.5 gm. (range 1.8 to 6.7 gm.) and 8.7 ± 2.7 gm. (range 5.5 to 13.6 gm.), respectively. In each case feces were collected during only one 3- or 4-day period. Annegers and associates[14] in a study of 40 normal subjects given 3000 calorie diets containing 93, 140 or 168 gm. fat (mainly lard or hydrogenated vegetable oil) found no significant differences in the fat excretion. By means of 5-day fecal analyses the daily total fat excretion was found to be 3.91 ± 1.56 gm. (range 0.79 to 7.03 gm.). The increase in fat excretion at higher levels of intake observed by Wollaeger and associates suggests that the fat intake was beyond the level of normal tolerance or possibly that the diet contained a larger proportion of high-melting-point fat.

Application of these methods provides the most satisfactory means of determining the presence of steatorrhea. Andersen and di Sant'Agnese[9], using 3-day fecal analyses, found a level of fat excretion in excess of 3 gm. per 24 hours in 58 patients with celiac disease, all of whom were given diets containing 50 to 70 gm. fat daily. It is a common practice to express fat absorption as a percentage, after the manner of a balance study[23, 28,51,219], that is, Per cent fat absorbed = $\frac{\text{Fat intake} - \text{Fat excreted}}{\text{Fat intake}} \times 100$. Cooke and associates[51] listed the findings of other authors and in their own study found that 95% or more (range 91 to 99%) was usually absorbed in normal subjects. Weijers and van de Kamer[219] found similar figures in adults and breast-fed babies and lower fig-

ures (about 85%) in babies on artificial food.

The studies of Hill and Bloor[105] in cats and of Annegers and associates[14] in normal human subjects, in which fat excretion was found unchanged at different and not immoderate levels of fat intake, imply that the fecal fat is not simply a nonabsorbed residue and render invalid the fat balance concept. Clinical experience suggests that the bulk of the excreted fat in the sprue syndrome is derived from fat ingested and that the fat balance concept thereby gains validity. There is evidence, however, in both celiac disease and in sprue that at higher levels of fat ingestion, within limits, the percentage fat absorption remains unchanged, that is, there is an increase in the absolute amount of fat absorbed as well as in the amount excreted[28,43,136,159]. Similar observations have been made in infantile diarrhea[42]. Hence, it is not the fat balance concept so much as the fat balance technique that is of value in determining the presence of steatorrhea. The method of van de Kamer and associates[118] of estimating the fat in wet feces as total fatty acid has proved satisfactory in clinical practice.

Radiology of the Small Intestine. The radiological appearances of the small bowel have been intensively studied in celiac disease[11,16,155], and in sprue[3,83,109,120,135,143,182]. Dilatation of portions of the intestine, particularly of the jejunum, ('moulage sign') and segmentation of the ileum with fragmentation or flocculation of the barium and with fluid levels are typical findings. With barium preparations which resist flocculation on the addition of mucus *in vitro* better filling of the intestine is obtained and a jejunal mucosal pattern with wide transverse bars in place of the normal feathery pattern is frequently seen[3,11,16,83,135]. This has been interpreted as evidence of excessive secretion of mucus in the sprue syndrome[16,83]. Marshak and associates[143] considered the changes characteristic and almost diagnostic of sprue and Hornsby and Baylin[109] believed that the presence of a 'deficiency pattern' (segmentation and fragmentation) tended to exclude a diagnosis of pancreatogenous steatorrhea.

Gastrointestinal roentgenographic studies also aid differentiation of the sprue syndrome from steatorrhea due to anatomic abnormalities of the intestine, for example, gastrocolic fistula, enteroenterostomy[66,101,165,181], ileocolostomy[34,66] and jejunal diverticulosis[62].

Hematologic Investigation. Anemia occurs so frequently in the sprue syndrome that its recognition is a material aid in diagnosis. It is generally agreed that in celiac disease the anemia, which may be mild or severe, is hypochromic and microcytic but that occasionally hyperchromic macrocytic anemia occurs[25,99,160,196,208]. The iron-deficiency type of anemia appears more commonly during the early and active phases of the disease and the macrocytic type during the later quiescent phases. Di Sant'Agnese[172] noted the frequency of macrocytic anemia in patients re-examined 3 to 11 years after the onset of the disease, whereas Gerrard and associates[87], in a similar study, noted hypochromic microcytic anemia. The latter was also the experience of Thaysen[208].

In the adult with nontropical sprue, Bennett and associates[25] and subsequent authors[20,52,53,100,114,166,183,208] found that the anemia varied in type. Iron-deficiency anemia with hypochromia and poikilocytosis, sometimes refractory to oral iron therapy[183], appears to occur less frequently than macrocytic anemia with variable depth of staining of the cells, poikilocytosis, the presence of target cells and a megaloblastic marrow. Cooke and associates[53] found macrocytic anemia in

two-thirds of their patients when first seen.

Hypochromic microcytic anemia is seen in the early stages of tropical sprue[195]. Macrocytosis, sometimes with hypochromia and with a megaloblastic marrow, develops rapidly and affects almost all patients[40,167,195,198]. Occasionally aplastic anemia may develop[195].

Other Procedures. In the sprue syndrome it is usual to carry out a glucose tolerance test. Flat blood glucose curves reflect delay in absorption and tend to confirm the absorptive deficiency of the small intestine.

Girdwood[89] noted a delay in the absorption of folic acid administered orally and assayed in the urine. This author proposed the use of folic acid absorption as a diagnostic test.

To differentiate between celiac disease and fibrocystic disease of the pancreas, duodenal intubation and assay of the enzymes in the duodenal contents are valuable procedures[9].

TREATMENT. In their response to treatment, celiac disease, nontropical sprue and tropical sprue differ to some extent from each other.

Celiac Disease. Gee[86] wrote, 'If the patient can be cured at all it must be by means of diet.' The diets employed in celiac disease have been various, but in general a diet high in protein and low in fat and carbohydrate content has been most favored. Fat in moderate amounts is well tolerated, but diarrhea and bulky feces follow excessive use[160]. Howland[111], in 1921, recognized that of all the dietary components carbohydrate especially caused rapid exacerbation of the disease process. Thus, he and others[102,103,160] excluded carbohydrate from the diet altogether in the initial stages of treatment. Haas[92] included ripe banana in the diet, the carbohydrate being in the form of invert sugar rather than in the form of starch, and for many years his diet was found a satisfactory regimen. It has become well established that carbohydrate has a detrimental effect upon fat absorption in celiac disease[8,133,175,178].

Having noted the effects of a scarcity of food during the famine in Holland (September, 1944, to May, 1945), Dicke[63] investigated the effects of different cereals in celiac disease. When wheat and rye flour were excluded from the diet, improvement was noted, and Weijers and van de Kamer[218] noted an increase in fat absorption. These findings were confirmed[12,64,177,184], and it was discovered that the detrimental factor, present in wheat, rye and oats but absent from corn (maize), rice and potato, was present in the gluten fraction (probably in the gliadin) and not in the starch fraction of wheat[12,119]. Wheat starch could be fed with no ill effect but the addition of wheat gluten (even as little as two slices of bread[176]) caused a prompt return of symptoms, diarrhea, and decrease in fat absorption[12,119]. A wheat gluten-free diet is followed by increased fat absorption within a few days, and clinical recovery is rapid. Ross and associates[170] found that 28 of 30 children with celiac disease responded to a wheat gluten-free diet. Of the 2 children who did not respond, one appeared to suffer from a deficiency of bile salts and the other had fat intolerance following an attack of gastroenteritis. Gerrard and associates[88] observed an equally striking response in 18 children and adolescents in whom celiac disease had been diagnosed 3 to 14 years earlier. Growth in weight and in height was greatly accelerated and steatorrhea ceased. It is not yet known how long the gluten-free diet should be maintained but it appears from long-term studies of celiac disease[87,172] that the diet should be continued until the growth period is over[87,176,177]. These observations are very remarkable.

In several instances of celiac disease associated with megaloblastic anemia a good response to folic acid has been reported[33,55,209]. When the marrow is normoblastic, as it commonly is, the response is poor[61].

Nontropical Sprue. Although most patients with nontropical sprue show some improvement on a diet high in protein, low in carbohydrate and fat, and supplemented by addition of calcium, vitamins and yeast, liver extract or folic acid, the period of treatment is long and the outcome is often disappointing. Folic acid usually controls the megaloblastic anemia but brings little improvement in fat absorption[18,61,73,221,227]. The observations of Gerrard and associates[88] in late celiac disease encourage the hope that these patients might respond to a gluten-free wheat diet, but the reported instances of satisfactory remission have hitherto been few in number[13,94,148,171].

During the past 4 years adrenocorticotrophic hormone (ACTH) and cortisone have been administered with dramatic results to patients with nontropical sprue refractory to other forms of therapy[1,7,19,46,50,117,124,134,150,163,204]. Appetite is improved, diarrhea is decreased and the patients have gained weight. In most cases there is evidence of improved absorption of fat, carbohydrate, vitamin A, nitrogen, calcium and iron. Megaloblastic anemia has been corrected by ACTH alone[150], and hypochromic microcytic anemia, refractory to oral iron therapy, has responded when cortisone was given in addition to ferrous sulphate[124]. The remission is not complete for the feces still contain a larger quantity of fat than is normal, and relapse tends to occur when administration of the hormones is discontinued. Long-term administration of ACTH or cortisone is advised[117]. Adlersberg and associates[2] found oral administration of hydrocortisone (Compound F) effective in inducing a remission when given in the form of the free alcohol, but ineffective in the form of hydrocortisone acetate.

Tropical Sprue. The employment of liver extract by Castle and associates[40] proved to be a great advance in the treatment of tropical sprue. In particular, anemia, glossitis and gastrointestinal symptoms are quickly relieved by liver extract administered parenterally or orally. Barker and Rhoads[22] noted an increase of fat absorption as judged by serum lipid curves, but Black and associates[27] observed only a small decrease in fecal fat excretion. These authors obtained a better response to yeast extract administered orally and considered that this was a dose effect, it being practicable under the circumstances to administer large quantities of yeast extract and only relatively small quantities of liver extract. Crude liver extracts in large doses have proved more effective than refined extracts in small doses. Black and associates were unable to induce a remission by the use of nicotinic acid and riboflavine.

In 1946 a further therapeutic advance of major importance was the introduction of folic acid by Spies and his colleagues[26,186,190] and by Darby and associates[56]. Folic acid, 5 to 25 mg., given parenterally or orally daily, brings about rapid relief of symptoms, cessation of diarrhea, gain in weight, and a return to normal of fat absorption[73,201], roentgenographic appearances of the intestine[201], glucose absorption curve[201] and vitamin A absorption curve[57]. Folic acid conjugates, administered orally, are equally effective[152,187,203]. Spies and associates[190] suggested that liver and yeast extracts were effective in proportion to their content of folic acid, which may explain why some patients fail to respond to liver extract but respond to folic acid[58]. With folic acid therapy no par-

ticular dietetic restriction is indicated. Indeed, in view of the severe malnutrition and hypoproteinemia which occurs, a liberal diet with a high protein content is advised[132]. Folic acid alone should not be relied upon in the treatment of tropical sprue. The remission provides an opportunity for improvement of the general nutritional status, and when the hematological remission is inadequate, liver extract, yeast extract or other hemopoietic agents should be added to the regimen.

The clinical and hematological effects of various hemopoietic agents have been explored in tropical sprue. Folinic acid, administered orally, has produced excellent clinical and hematological remissions[169,189,202]. With 5-methyl uracil (thymine), given orally in large doses, 15 gm. daily, the hematological response is good but the clinical response poor[185,193]. Hematological and clinical remissions have been obtained with vitamin B_{12} when administered parenterally[188,192,200]. Spies and Suarez[192] stated that relapse occurred quickly when vitamin B_{12} administration was discontinued and that subsequent response to folic acid was excellent. No remission is obtained when vitamin B_{12} is administered orally in doses up to 300 micrograms daily[168,191] or when administered sublingually[199].

The sprue syndrome in general is typified by the occurrence of multiple avitaminoses, and the megaloblastic anemia appears to provide no exception[166]. Nieweg and associates[158] divided megaloblastic anemias into those deficient in vitamin B_{12} and those deficient in folic acid. To the first category belong some cases of nontropical and tropical sprue[192] and to the second the majority of cases of tropical sprue and those cases of nontropical sprue in which the anemia is resistant to vitamin B_{12} but responds to folic acid[45,114,211]. In many instances of tropical sprue a better hematological response is obtained when both vitamin B_{12} and folic acid are employed[191]. Clinically, neurological complications are associated with vitamin B_{12} deficiency. Davidson and Girdwood[60] and Ungley[213] have reported patients with megaloblastic anemia in the sprue syndrome in whom neurological lesions developed during treatment with folic acid.

Keele[122] found sulfaguanidine helpful in controlling watery diarrhea in sprue, but there have been reports during the past year of a striking remission in the sprue symptoms, anemia and steatorrhea, following the administration of aureomycin[13,173] and of chloramphenicol, streptomycin, penicillin, and sulfasuxidine[13]. Weijers and van de Kamer[220], however, did not find improvement in fat absorption in celiac disease treated with streptomycin.

PATHOGENESIS. A consideration of the pathogenesis of the sprue syndrome is hampered to a great extent by the scanty evidence of any pathological lesion[131]. Indeed, evidence of malabsorption by the small intestine in the absence of a demonstrable cause has been held important in establishing the diagnosis of sprue[53]. There is no gross destructive lesion of the small intestine: 'Naked-eye examination of dead bodies throws no light upon the nature of the coeliac affection' (Gee, 1888). Milanes and associates[151] have reviewed the few microscopic reports and have described a biopsy specimen from the jejunum of one of their patients. Atrophy of the mucosa and muscular layers and degenerative changes in the neurones of Auerbach's plexus were found, and the authors postulated that these changes might reflect the deficiency of absorption and intestinal motor dysfunction characteristic of sprue.

Bennett and Hardwick[24] recognized that a clinical condition simulating sprue, namely, steatorrhea with macrocytic anemia, tetany, and the manifestations of a deficiency of various vitamins, arose in some patients with gastrocolic fistula and enteroenterostomy and in patients in whom the intestinal lacteals were involved by fibrotic tuberculous lesions or lymphomatous lesions. Correction of the fistulae by operative procedures produced an immediate amelioration of the 'secondary sprue' symptoms, an experience noted by many subsequent observers. Bennett and Hardwick concluded that 'chronic jejuno-ileal insufficiency' of a functional nature was the basis of the sprue syndrome.

This insufficiency is now known to involve malabsorption of many substances besides fat and vitamin A. For this reason, the term, nontropical sprue is preferred to idiopathic steatorrhea. The defect of absorption is partial and by the technique of the blood curve it is manifested mainly as delayed absorption. Flat blood glucose curves have been observed by many investigators and are attributed both to delayed and to diminished absorption[74,80,96,107,137,179,205]. The absorption curve of fructose, at one time considered normal[137], has been shown to be flatter and more prolonged in the sprue subject than in the normal subject[70,74]. Xylose[71], rhamnose[39], glycine[68], urea[80], folic acid[89], radioactive iron[20,56], and radioactive sodium[157] are poorly absorbed. By metabolic balance methods Comfort and associates[48] have demonstrated abnormally high fecal excretion of phosphorus, chloride, sodium, and potassium. Wollaeger and Scribner[225] noted a defect in water absorption, which they attributed to the bulky intestinal contents. The clinical picture suggests defective absorption of several vitamins, particularly of the fat-soluble vitamins, D and K.

Many theories have been propounded to explain the nature of the fundamental defect in sprue, and it is feasible here only to indicate the principal trends of current thought.

a. A Metabolic Disorder. Weijers and van de Kamer[220] noted that patients with celiac disease always excreted more saturated than unsaturated fatty acids. When the dietary fat consisted of olive oil (containing only about 10% saturated fatty acids), the fecal fat excretion became normal. The effect of a diet containing wheat flour was to increase the excretion of saturated fatty acids without affecting unsaturated fatty acid excretion, so much so that with a wheat flour-olive oil diet more saturated fatty acid was excreted than was contained in the diet. These authors then fed their patients on a wheat flour-fat free diet and found once again the excretion of saturated fatty acids in considerable quantity. They therefore concluded that in celiac disease there was a fundamental disturbance of intermediary fat metabolism.

When Weijers and van de Kamer fed their patients a diet containing olive oil as its fat moiety, they noted a very distinct improvement in the clinical condition and a return of the stool to normal in odor, color and consistency. It appears possible that this was the experience of those who have described allergy to cow's milk as a cause of celiac disease[116,126,147], that is, improvement followed withdrawal from the diet of butter fat, having a high content of saturated fatty acids. Moreover, having regard to the occurrence nowadays of celiac disease in early infancy, which Andersen and di Sant'Agnese[9] attribute to artificial feeding, the possibility must be entertained that cow's milk and artificial food may, in some instances, contain a protein substance

capable of acting in the manner of wheat gluten. Skin testing with the gliadin, globulin, glutenin and proteose fractions of wheat gluten has not proved of value in the diagnosis of celiac disease[47].

In several cases of adult sprue, Jiménez Diáz and associates[115] found more fat excreted in the feces than was eaten in the diet. It would be interesting to know whether the excreted fat was composed principally of saturated fatty acids, and the effect of wheat gluten and of rancid fat[84] upon fatty acid excretion in adult patients.

b. A Cellular Defect. To many, the malabsorption defect in sprue is suggestive of an intrinsic cellular defect. Verzar and McDougall[214] and Stannus[194] attributed the failure of glucose and fat absorption to failure of phosphorylation within the mucosal cells. Stannus[194] implied that the deficiency of phosphorylating enzymes was related to a deficiency of B group vitamins. Badenoch and Callender[20] have tentatively suggested that a deficiency of apoferritin production might account for the defect of iron absorption. Undoubtedly, in conditions of severe undernutrition, protein synthesis is defective and so also may be enzyme synthesis.

Verzar and McDougall[214] found phosphorylation defective after adrenalectomy, but adrenal insufficiency has been disregarded as a primary factor in the sprue syndrome, since steatorrhea is not typical of Addison's disease. It is of interest that ACTH and cortisone were administered to patients suffering from nontropical sprue, not as replacement therapy but in the hope that cellular activity might be modified. The dramatic response to these hormones has been interpreted by Jones[117] to mean that in nontropical sprue there exists a fundamental absorptive defect due to a disturbance in intestinal mucosal cell dynamics.

Rodriguez-Molina[167] has indicated a similar response in tropical sprue, but so far no definitive studies of a clinical trial of the corticosteroids in tropical sprue have been published.

c. A Deficiency Disorder. In nontropical sprue deficiency of fat-soluble vitamins (A, D, K) and of water-soluble vitamins (riboflavine, nicotinic acid, folic acid, B_{12}) may frequently be relieved without much effect upon fat absorption. With the exception of folic acid, this is also true of tropical sprue. Castle and associates[40] believed that liver extract supplied an essential factor, Black and associates[27] noted that yeast extract also contained this factor and Spies and his colleagues[190] attributed tropical sprue largely to a deficiency of folic acid. Stefanini[195] has discussed the evidence and concluded that tropical sprue in his Italian prisoners-of-war was due to dietary deficiency.

It is, in many instances, difficult to ignore the similarity of tropical sprue to nutritional macrocytic anemia and to the clinical state of the victims of famine. Rao[164] produced a sprue-like syndrome with intestinal mucosal atrophy and malabsorption in monkeys by feeding them a diet deficient in protein and vitamins.

d. A Mechanical Defect. Several authors[13,90,112] have put forward the view that the defective absorption of the sprue syndrome is a result of motor dysfunction of the small intestine or of defective pumping action of the villi. Cummins and Almy[54] studied the absorption of methionine and glucose from segments of the small intestine isolated by means of balloons. A suggestive increase in absorption was noted in normal subjects and in sprue patients under conditions of increased intestinal motility, induced by mecho-

line and physostigmine, which the authors considered might be related to increased intestinal blood flow. Absorption was not apparently diminished by the hypomotility induced by banthine and the authors concluded that hypomotility was not the primary cause of defective glucose absorption in the sprue syndrome. De Langen[128] studied meteorism, in particular, and suggested that the defective absorption of gases, as of other substances, was related to poor circulation of blood in the intestinal capillary bed.

Frazer[79] has summarized his views in stating that "the sprue syndrome is induced by certain dietary factors which cause increased mucus secretion, decreased motility and altered bacterial growth in the upper intestine. The resultant delay and depression of absorption favors further bacterial changes and the establishment of a vicious circle that can only be broken by dietary restriction, or control of intestinal flora."

The radiological appearance of the small intestine in sprue has been attributed in large measure to the presence of excessive mucus secretion[16,83]. By duodenal intubation after a test dose of 100 ml. olive oil, Smart and Daley[180] found the chyme in normal subjects to consist of a uniform oil emulsion. In sprue subjects, on the other hand, the chyme consisted of clumps and threads of mucilaginous material in which emulsified droplets of fat were enmeshed. These authors considered that the excessive mucus secretion interfered with contact between fat particles and the mucosa. Frazer and associates[80] found glucose and urea absorption from the upper part of the small intestine depressed to a like degree in 10 cases of the sprue syndrome. This observation was interpreted by the authors to exclude faulty phosphorylation and bacterial destruction of glucose as causes of the defective glucose absorption, since both glucose and urea absorption were equally affected. They suggested that the absorptive defects might be due to excessive mucus secretion, hypomotility of the intestine, or to both of these factors together. Similarly, Wollaeger and Scribner[225] attributed faulty water absorption to the presence in the intestine of abnormally bulky contents.

There is, therefore, good evidence of the importance of intestinal dysfunction and of interference with absorption by the contents of the intestine in the sprue syndrome. The main difficulty arises in accepting these as primary causes of sprue. The conclusion appears reasonable that the dietary factors (wheat gluten, rancid fat) are effective in initiating these changes in subjects who are especially susceptible, or, in other words, in whom the sprue defect is already present.

e. A Change in the Bacterial Flora of the Intestine. Tropical sprue tends to occur in outbreaks, sometimes of an epidemic character[130,141,215], and an infective origin has been postulated[141]. However attractive such an hypothesis may be, direct evidence of a bacterial or virus agent is lacking. Leishman[130], however, has suggested that a change in the bacterial equilibrium within the lumen of the intestine could affect the synthesis of the B group vitamins and hence, bring about indirectly a deficiency disorder manifesting itself as the complex sprue syndrome. Support for this suggestion is provided by the response to antibiotic agents[13,122,173]. Foy and Kondi[75] have described the response of African patients with megaloblastic anemia to penicillin.

Experimentally, it has been noted that the megaloblastic anemia, produced by the formation of intestinal culs-de-sac in rats[38,216], responds well to administration of folic acid and aureomycin[217] but poorly to the use of liver

extract and vitamin B_{12}[37]. In these rats there is defective fat absorption whether or not anemia develops[6]. Woll and Oleson[222] fed folic acid antagonist (aminopterin) to rats and produced a maturation arrest of the red cells, sometimes progressing to aplastic anemia, and atrophy of the mucosa of the small intestine, which changes the authors considered comparable to sprue.

It seems not improbable that the megaloblastic anemia that may develop in patients who have undergone intestinal short-circuit operations may depend upon changes in the bacterial flora. Response of this anemia to folic acid has been noted but, so far, there have been no reports of the effect of antibiotic agents in these patients. Foy and Kondi[75] state that variations in the diet produce great changes in the intestinal flora, that dextrin encourages a denser flora than does sucrose, and that rancid fats produce a profound effect upon the ecology of the intestinal organisms. It is known that a change of climate or of altitude, alone may greatly benefit a patient suffering from tropical sprue and this, perhaps, is effective through a change in the intestinal flora.

Frazer[77] has discussed vitamin deficiency in sprue, and has attributed a deprivation of vitamins to competition between exuberant intestinal bacteria and the host. This hypothesis was supported by finding evidence of invasion of the upper intestinal tract, during a sprue relapse, by organisms normally confined to the lower portions of the tract. This invasion he considered one of the consequences of the presence within the upper intestinal tract of excessive mucus and nonabsorbed food material and, in some cases, of fixation of the pH because of achlorhydria.

Whereas the evidence strongly supports the view that changes in the intestinal flora are of a secondary nature in the sprue syndrome, it is of interest to note that antibiotic agents (sulfaguanidine[110], chloramphenicol, aureomycin and terramycin[149]) have been held responsible for the development of chronic diarrhea and steatorrhea.

Summary and Conclusion. The sprue syndrome comprises celiac disease, nontropical sprue and tropical sprue. Although the syndrome has long been recognized, its present incidence appears to be greater than was formerly suspected, probably as a result of increasing awareness of, and interest in, the condition and recognition of latent sprue. A heredo-familial incidence is recognized. No single criterion serves to make a diagnosis. It is first suspected on clinical grounds and its establishment is aided by demonstrating excessive excretion of fat in the feces, by radiology of the small intestine, and by hematological examination.

During the last 10 years there have been therapeutic advances of major importance, not only of themselves but also because these have promoted some clarification of the problem of the pathogenesis of the sprue syndrome. The long-recognized deleterious effect of carbohydrates in celiac disease is now known to be an effect of the gluten fraction of wheat, rye and oats. The majority of patients with celiac disease and several with nontropical sprue respond to a gluten-free wheat diet. In other patients with nontropical sprue refractory to treatment, dramatic remissions have followed administration of ACTH and cortisone, but relapse tends to occur on withdrawal of these hormones. In tropical sprue clinical and hematological remissions are obtained with folic acid or folinic acid. Alone, these may not produce adequate hematological remission and require the addition of vitamin B_{12}, liver or yeast extracts. A recent and interesting development is the effective remission produced

by administration of antibiotic agents.

The sprue syndrome is complex by reason of the manifold signs of deficiency that may develop during its course. It is a clinical syndrome of intestinal malabsorption that appears to be initiated in several ways. In celiac disease there appears to be a latent fundamental defect of fat metabolism at the level of the intestinal mucosal cells, a concept favored by the heredofamilial incidence. Many examples of nontropical sprue are old cases of celiac disease, often refractory to treatment. In tropical sprue a deficiency of folic acid appears to cause megaloblastic anemia and atrophic changes in the small intestinal mucosa. The fundamental defect in celiac disease is aggravated by diets containing wheat gluten, and in tropical sprue, possibly, by rancid fat. Hypomotility of the bowel, stagnation of the intestinal contents and excessive mucus secretion further interfere with the absorption of many substances (which may already be poorly absorbed) and promote an exuberance of the intestinal flora of organisms. These, in turn, compete for the available B vitamins and the condition worsens in the manner of a vicious circle.

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NEUROLOGY AND PSYCHIATRY

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FAINTING: A REVIEW OF THE NEUROPSYCHIATRIC ASPECTS

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IN clinical practice fainting and syncope are used as essentially equivalent and interchangeable terms to describe relatively brief interruptions of consciousness. When loss of consciousness is secondary to organic brain disease or represents a manifestation of epilepsy such terms as stupor and coma, automatism, petit mal absence and the like are believed to be more appropriate. This exclusion of transient loss of consciousness secondary to epilepsy or organic brain disease from the category of fainting or syncope is generally valid and clinically justified. However, there are situations in which the differentiation is difficult, as will be reviewed below.

The first comprehensive modern discussion of fainting was that of Weiss[25] The definitive work, however, is that of Engel[5], a monograph entitled *Fainting*, published in 1950. This book was completed in 1948 and includes not only a good review of the literature through 1947, but also reviews much original work by Engel and his coworkers. This book still represents the "last word" on the syncope problem, and it is highly recommended as a very readable and practical discussion of the subject. A slightly more recent and somewhat briefer review is that of Stead[22]. It will not be the purpose of this article to attempt a condensation of either of these excellent works. Rather, an attempt will be made to clarify and underline some of the neuropsychiatric aspects of fainting, as well as to review certain of the literature that has appeared since these reviews were written. In addition, a brief excursion will be made into the field of epilepsy, particularly as it relates to those conditions featured by brief lapses of consciousness and not readily differentiated from syncope.

VASODEPRESSOR SYNCOPE. The terms *syncope* and *fainting* generally include transient spells of giddiness and lightheadedness, as well as conditions in which consciousness is completely lost. Statistically speaking, so-called vasodepressor syncope is probably the most common form of fainting[5]. Characteristically this is the type of fainting occurring in situations in which the person becomes suddenly fearful and yet cannot flee. The young draftee who falls down in line just before having a specimen of his blood drawn would be a good example. The setting is us-

ually one of real, threatened or fantasied danger, in which the threat must be denied or at least cannot be escaped[7]. Physiologically there appears to be a shunting of blood into the muscles as if in preparation for activity. However, an inhibition of subsequent muscular movement occurs. In addition there appears to be a failure of the usual cutaneous and visceral compensatory vasoconstriction with which we ordinarily react to threatening situations. One recent study[20] indicates increased cutaneous heat elimination prior to fainting. This would actually suggest increased blood flow in the skin prior to such faints. All of this indicates an inappropriate response to a frightening situation with the person preparing to flee and yet inhibited by circumstances from doing so. The resulting surfeit of blood in the muscles and failure of compensatory vasoconstriction elsewhere produces, then, a marked drop in blood pressure, particularly within the arteries of the brain, and a decrease of blood flow within the brain. The resulting sudden feeling of light-headedness is frequently followed by the person slumping to the ground and losing consciousness briefly. If the failure of cerebral circulation is sufficiently marked and prolonged, there may even be a few clonic convulsive movements often leading to the erroneous diagnosis of an epileptic seizure. Vasodepressor syncope is frequently seen at blood banks, where on the average between 4% and 5% of donors reportedly faint[3]. Occasionally this is prior to the donation of blood but usually afterwards.

HYSTERICAL SYNCOPE. Another common form of fainting is frequently encountered as one of the manifestations of conversion hysteria. The typical conversion hysteric attempts to find expression of underlying and unconscious conflicts in the form of substitute or symbolic acts such as fainting[18]. One of the most lucid statements concerning the meaning of hysterical attacks, including hysterical fainting, is that of Freud[11], published in 1909, "When we psychoanalyze a patient subject to hysterical attacks, one soon gains the conviction that these attacks are nothing but fantasies projected and translated into motor activity and represented in pantomime." He notes further that these fantasies are often of the same order as seen in dreams and thus subject to the same degree of distortion. Therefore, it may not be readily discernible on the surface just what the hysteric is attempting to express symbolically in the fainting attack. He points out that such attacks may be "aroused" by some event in the immediate environment which associatively stirs up the content of certain repressed complexes, usually sexual in nature. In this case the fainting may represent a "flight into illness" in the face of stimulating, painful or frightening reality. In certain females we may see the faint as a symbolic expression of, or substitute for, desired sexual experience, and also a protective negation of such desires. Hysterical fainters are quite likely to repeat their performances, and we often suspect that the actual gain they receive in terms of attention and care from those about them may become an important determinant in the production of subsequent fainting spells[9]. This brings up the added problem that we often encounter clinically of differentiating between hysterical fainting in which the conflicts are unconscious, and deliberate, consciously determined "blackout spells" which are examples of malingering.

VASODEPRESSOR VERSUS HYSTERICAL SYNCOPES. In the last 10 years there has been considerable clarification of certain of the basic concepts of psy-

chosomatic medicine, particularly in regard to the differentiation between hysterical and vegetative neurotic disorders. In the latter, dysfunction of the autonomic nervous system plays a role: asthma, peptic ulcer, and others. Much of the best and most basic thinking has been done by Alexander and his co-workers[1] at the Chicago Institute. This differentiation is quite apropos to the problem of vasodepressor syncope versus hysterical syncope. There is much in vasodepressor fainting spells to suggest a vegetative dysfunction. As already noted, there is an abrupt disturbance in the distribution of blood in the vascular bed with very low cerebral blood pressure and reduced blood flow with a loss of consciousness and a concurrent slowing demonstrable in the electroencephalogram[18]. The basic difficulty in vasodepressor fainting appears to be that of control and coordination of functioning within the systemic vascular system, a system which is not significantly under the control of the voluntary nervous system. The resulting syncope is *not* a substitute or symbolic expression of an emotion, as with hysterical fainting, but is rather a physiological concomitant. Initially, at least, the vasodepressor reaction does not relieve repressed feelings but is secondary to the physiological response of the organism to certain emotionally charged situations. There may or may not be important neurotic determinants functioning in the person who has a vasodepressor faint. For example, if the individual faints as a reaction to sudden pain as from a turned ankle or any painful and frightening injury, this is not necessarily indicative of important psychogenic determinants. Oftentimes vasodepressor syncope is a "first time" phenomenon, and the individual may again face the same stress and not faint. This is well demonstrated in the medical student who may faint at the time of his introduction to the cadaver or at his first necropsy but then functions well subsequently at the operating table. On the other hand, we see many persons who show typical vasodepressor attacks repeatedly and often in situations in which we can objectively see very little that would constitute a justifiable source of stress. As Romano and Engel[18] point out, repeated vasodepressor attacks are frequently seen in males in whom there appears to be an excessive amount of generalized anxiety concerning bodily function and excessive fear of bodily injury ("castration anxiety"). These people will often faint with any bruise, cut or threatened injury to the body or at the sight of blood. This certainly suggests that not only the nature and amount of noxious stimuli but also the personality structure of the individual can be important theoretical determinants in producing vasodepressor syncopal attacks.

Thus, in attempting to differentiate between fainting as a manifestation of conversion hysteria and as a vasodepressor (vegetative) phenomenon, an important feature is the basic personality of the individual involved. The hysterical fainter often demonstrates an immature, childish, "acting-out" personality, met with clinically more often in women. One frequently sees the hysterical spell occurring in the presence of others, in an abrupt and dramatic manner. A general indifference to the symptom (*"la belle indifference"*) is frequent with the hysterical fainter and unusual with the vasodepressor one. Unfortunately the matter is often not so simple and clear-cut. Conversion as a mechanism (with hysterical fainting as a manifestation) is at times seen in individuals who do not demonstrate the classical hysterical personality. In addition, it is not uncommon to see vasodepressor faints in

basically hysterical individuals who show other manifestations of conversion (paralyses, disturbances in sensory functioning, and the like). In such cases the faint may not have the initial symbolic meaning a hysterical faint would have in the same individual. In short, the hysteric may also become frightened and be unable to flee, reacting then, in that situation, like the nonhysteric.

Assuming that one is able to make a reliable differentiation between these two very common types of syncope, the problem of therapy arises. Generally the immediate therapy of the unconscious individual is not a major problem, since his recovery is usually very prompt; in the case of vasodepressor syncope within a few seconds. For the vasodepressor faint the classical "head-between-the-knees" type of therapy is only of minimal assistance, and it appears to be much more sensible to place the person in a supine position with the legs up if possible. If aspiration is feared, the patient can be placed in a prone position[21]. In the management of the hysterical faint it is well to make the individual as comfortable as possible and then to step back and add as little of the dramatic to the situation as possible. This will at least tend to reduce the degree of "secondary gain."

As far as more long-term treatment is concerned, such a discussion is essentially beyond the scope of a review paper. Most cases of vasodepressor syncope do not represent chronic, recurrent problems. The same is true of the hysterical fainter, and when the hysterical syncopal attacks become an important clinical problem there are usually many other hysterical manifestations present which lead to this person being referred to a psychiatrist for more comprehensive evaluation and therapy. Drug therapy has very little to offer in either hysterical or vasodepressor syncope, except occasionally in the hysteric when coupled with rather intensive psychiatric help.

OTHER TYPES OF SYNCOPE. There are a number of other types of syncope which, while not nearly as common as hysterical and vasodepressor, are of interest and importance in neuropsychiatric work. *Orthostatic hypotension* is often accompanied by syncope when the individual rises suddenly from the recumbent or sitting position. When this condition is suspected clinically, it is easily demonstrable by use of the blood pressure instrument. This condition is occasionally seen in chronic anxiety states[5], in certain organic diseases such as Addison's disease, and others. With the widespread use of rauwolfia derivatives and chlorpromazine in psychiatric practice, this type of reaction may be seen more frequently, particularly after the parenteral administration of such drugs. There is, in addition, an interesting clinical entity called "*chronic orthostatic hypotension*" in which the blood pressure of the individual falls rapidly to below 60 mm. Hg on arising. Stead and Ebert[23] showed that this is due to an absence of normal vasoconstriction elsewhere in response to pooling of the normal quantity of blood in the lower extremities (that is, it is not due to abnormal pooling in the lower extremities). It is frequently associated with diseases of the central nervous system such as tabes dorsalis and encephalitis and may occur in traumatic spinal cord lesions, syringomyelia and the like. A recent case report from England[4] points out the frequency of a clinical triad of: 1) a profound fall in blood pressure on standing, 2) anhydrosis, and 3) impotence. Interestingly, very extensive sympathectomies may produce a very similar picture.

The *carotid sinus* has received much

attention through the years as a cause of several types of syncopal attacks. Weiss[25] felt that stimulation of the carotid sinus could produce syncope through 1) cardio-inhibition, 2) vasodepressor response, or 3) a reflex cerebral type of response. In actual practice he felt that the majority of people who became unconscious due to a hyperactive carotid sinus became so because of a combination of these effects. Greenblatt and co-workers[13] studied this problem and reported in 1949 on "600 Positive Central Nervous System Responses to Carotid Compression." They conclude that the cardiac effects (3 to 5 seconds of asystole) are due to a true reflex which can be blocked by atropine or novocaine. They feel that the cerebral effects with carotid compression are due simply to the decrease of circulation to the brain. They are inclined to doubt a true cerebral reflex. To support this they note that the same electroencephalographic changes occur whether compression is at or below the sinus, and that these changes are not blocked by novocaine locally or atropine systemically.

It should be noted at this point that syncopal spells may be the forerunner of a cerebral vascular attack which will later produce clear-cut neurological residuals. On the other hand, syncopal attacks may be a manifestation of what Alvarez[2] has repeatedly referred to as "the little strokes." The loss of consciousness here may be due to a disturbance in the blood supply to the vasomotor centers in the brain stem or to portions of the reticular formation of the upper brain stem, which Penfield[16] has referred to as the "centrencephalic system." This he believes is the center of consciousness, the "highest level" of functional integration.

Obstruction of the common carotids secondary to a syphilitic or arteriosclerotic process may produce transient loss of consciousness[22]. Obstruction of the vertebral arteries, the basilar artery or one of its branches can produce loss of consciousness which may be transient if the disturbance of circulation is brief and intermittent. An interesting example of this was reported by Ford[10] in the case of a young man who had a defect of his odontoid process with excessive mobility of the second cervical vertebra. This boy had intermittent syncope with periods of unsteadiness, nystagmus and diplopia. At times this could be precipitated by pushing the head forward. Complete relief of symptoms was obtained following a fusion of the upper cervical spine. Interestingly the correct diagnosis was not made until a chiropractor characteristically suggested a cervical spine defect. Reported cases of syncope following vigorous spinal manipulation may also be on the same basis (that is, compression of the vertebral arteries). Patients with subtentorial tumors will occasionally present a history of sudden falling with loss of consciousness which may also be the result of interference with blood supply to the brain stem from the expanding lesion[17].

The patient with a *chronic hyperventilation syndrome* frequently complains of attacks of light-headedness, dizziness, and fainting, in addition to concerns about breathlessness, smothering, numbness and tingling of the extremities, and the like. Actually it is very unusual to find a complete loss of consciousness and falling with hyperventilation. When syncope is a part of the chronic hyperventilation syndrome careful history usually indicates numbness, tingling, light-headedness, prior to the loss of consciousness, and the latter is usually not total. Engel *et al.*[6] have effectively reviewed the clinical symptomatology of hyperventilation and have underlined the fact that when syncope is seen as part of this

syndrome it is usually on the basis of a concurrent vasodepressor syncope or a hysterical type of fainting. They have found, however, that a reduced level of awareness during overventilation, when present, can be correlated with the degree of slowing in the electroencephalogram. They note, in addition, that an individual with a low blood sugar is more susceptible both to a lowering in his level of awareness with overventilation and to slowing in his electroencephalogram.

Hypoglycemia by itself may result in syncope, but according to Stead[22], "Sudden, transient loss of consciousness without any other symptoms has not in my experience been caused by hypoglycemia." However, a sequence of difficulty in concentration, light-headedness, disorientation, amnesia, followed by unconsciousness and at times convulsions is not uncommon with hypoglycemia. Such hypoglycemia usually occurs several hours after eating. It may occur in diabetics who have taken too much insulin, in persons with islet cell tumors, occasionally in cases of functional hyperactivity of the islet cells, and at times in people with adrenal cortical insufficiency.

Recently there has been a revival of interest in the mechanism of fainting following coughing: *tussive syncope*. Sharpey-Schafer[19], a British author, points out the frequency with which this is encountered and reviews the mechanism by which the coughing results in an acute diminution of blood supply to the brain. His review of 27 cases indicates that violent coughing is the determining factor and that only usual physiological mechanisms are involved. Continuous coughing without the individual drawing a breath is somewhat similar to the Valsalva experiment and results in intrathoracic pressures of 200 to 300 mm. of Hg being reached. Consciousness is lost usually during the period of acute hypotension following cessation of the coughing. His cases are almost entirely in middle-aged males without pulmonary disease. It is implied that the coughing represents a "habit" and that attempts to remove irritative factors will not be successful, nor will explanations to the patient of the mechanism involved be helpful. It would be interesting to speculate what psychological determinants may be behind a "habit" which results in repeated bouts of unconsciousness. (It should be noted that one occasionally sees epileptic seizures which are ushered in by a cough-like cry. This should not cause any great difficulties in differentiation, however, since the cough is never of the severity encountered with tussive syncope.) Tussive syncope is seen occasionally in children with pertussis and in adults with chronic laryngitis and bronchitis.

Estes and his group at Duke[8] have recently suggested that there may be a further physiological mechanism of importance in tussive syncope. It appears highly likely that increased intrathoracic pressures are transmitted directly to the cerebral spinal fluid. They have reported pressures as high as 300 mm. Hg in the cerebral spinal fluid during such coughing episodes. This would suggest that arterial inflow to the brain is impaired and that blood may actually be squeezed out to other areas.

Two interesting variations of tussive syncope are reported from England[14]. One is the so-called "mess trick" in which the voluntary victim is persuaded to hyperventilate and then has his chest suddenly compressed by someone standing behind him. If he keeps his larynx closed he will frequently lose consciousness for a few seconds. The other variation is referred to as the "fainting lark" in which a boy squats and takes 20 or so deep breaths and then rises quickly and, as he does so, closes his nostrils with his fingers and

blows hard (Valsalva's Experiment). With these tricks the loss of consciousness is very brief but one can imagine considerable consternation being produced by them in a small classroom, or during a brief recess period.

It should be pointed out that I have not attempted to cover every aspect of the fainting problem. No reference has been made to syncope secondary to cardiac standstill, anoxemia, cardiac disease *per se* (*cf.* aortic valvular disease, paroxysmal tachycardias, and others). This is not meant to imply their lack of general clinical importance. They are not, however, of primary interest to the neuropsychiatrist, and little if any significant literature has appeared covering them since the Engel[5] and Stead[22] reviews.

SYNCOPE VERSUS EPILEPSY. I wish to conclude this review with a brief discussion of states in which there is brief loss of consciousness on the basis of paroxysmal discharges within the brain itelf (for example, epilepsy). Such lapses of consciousness are not considered examples of fainting or syncope. However, despite advances in clinical epileptology and electroencephalography in the last 10 years, we are still unable at times to differentiate between certain cases of syncope proper and certain epileptic attacks. Usually, however, this is readily done, as witness petit mal epilepsy, which, while featuring brief lapses of consciousness, is seldom confused with fainting attacks.

In a very comprehensive and careful study in 1949, Kershman[15] reported on a group of 114 patients who had both the history of syncopal attacks and abnormal interseizure electroencephalograms. He points out how often syncope can be "cerebral in origin and epileptic in character." He points out the difficulty in differentiating between such syncope and "vasomotor fainting" (*cf.* vasodepressor syncope). He points out that temporal lobe epilepsy accounts for only a small percentage of these (6%) and feels that the great majority are caused by paroxysmal discharges from the gray matter in the vicinity of the third ventricle. Many of his patients demonstrated the features of vasomotor hyperactivity so that a hypothalamic locus seems reasonable. He has suggested the term *encephalosyncope* to avoid the stigma of epilepsy. Sir Charles Symonds[24] similarly speaks of localized paroxysmal discharges within the areas of the brain, where consciousness is located, as a cause of syncope. He points out the difficulty in differentiating these attacks from vasodepressor syncope, at least by history. He makes the point that minor clonic movements cannot be taken as evidence of the syncope being epileptic in nature, since approximately 7% of persons who have clear vasodepressor attacks will demonstrate such movements. As mentioned above, Penfield[16] has attempted to localize consciousness in the reticular formation of the upper brain stem, which he refers to as the "centrencephalic system." Epileptic spells featuring loss of consciousness, according to this group, can be expected whenever the function of this system is disturbed either by paroxysmal discharges within it or from outside firing to it.

Gibbs and his co-workers[12] have reached much the same conclusions as Kershman[15]. They have written extensively concerning what they refer to as 14- and 6-per second positive spikes appearing in the electroencephalograms of certain individuals during sleep. From experimental work on animals and from clinical considerations they believe that this pattern is highly suggestive of thalamic or hypothalamic disturbances. In a series of 427 cases in which 14- and 6-per second positive spikes were seen, 128 or 30%, had syncopal-like spells as the type of clinical seizure. Such attacks of unconscious-

ness generally last 30 seconds or longer and are unassociated with convulsive movements. They point out that such spells can be distinguished from vasodepressor fainting by the fact that they are unrelated to posture and so can occur with a patient recumbent and are unrelieved by lying down. In addition, loss of consciousness associated with 14- and 6-per second positive spikes generally lasts somewhat longer, and may even persist for several hours. These spells are usually followed by drowsiness and frequently associated with headache. In addition to loss of consciousness seen in patients with the characteristic electroencephalographic pattern of 14- and 6-per second spiking, Gibbs *et al.*[12] note that 50% of patients with focal seizures and an associated mid-temporal electroencephalographic focus lose consciousness early in the attack. They point out that this loss of consciousness may be the only symptom.

Thus it appears clear that there are occasional cases of fainting in which the electroencephalographer, the neurologist and neuropsychiatrist may be helpful in determining whether the loss of consciousness is on the basis of one of the types of syncope already discussed or whether it represents the result of a paroxysmal discharge within the brain, that is, an epileptic phenomenon. A careful history and the opportunity to observe the spell are usually sufficient to differentiate, but this is not always true. With careful electroencephalographic and neurologic study a certain number of cases of loss of consciousness previously ascribed to vasodepressor syncope or hysterical fainting will undoubtedly be found to represent epileptic manifestations. On the other hand, careful psychiatric study of a certain number of cases believed to be clearly epileptic in nature with involuntary passage of urine and tongue biting will be found to be examples of hysterical syncope rather than epilepsy. As Freud[11] pointed out a half century ago, tongue biting "is no more inconsistent with hysteria than with love-making."

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BOOK REVIEWS AND NOTICES

PATHOLOGY. BY PETER A. HERBUT, M.D., Professor of Pathology, Jefferson Medical College. Pp. 1227; 1378 ills., Philadelphia: Lea & Febiger, 1955. Price, $16.00.

THIS is the third major text in Pathology written by an American author in just over ten years. Like the two which came out earlier it is a complete catalogue of human diseases; indeed, because of the succinct and unpadded manner in which it is written, it is probably more complete insofar as it includes even a greater number of disease entities. The material is arranged in much the same order as most of the classic texts on this subject though Dr. Herbut inserts a useful chapter on the necropsy in the early portion of the book. Some may offer the criticism that the portion dealing with "general pathology" constitutes only about one-eighth of the whole, whereas many pathology teachers feel that it should make up at least a quarter of the basic course. The greater portion of the book deals with the pathology of the various systems, beginning with the cardiovascular and proceeding in the customary order. Each disease entity of importance is considered in the rather rigid sequence of etiology, pathology, complications, clinical aspects, diagnosis, treatment and prognosis with, of course, the emphasis on the gross and microscopic pathology. Little space is allotted to the variations in opinion concerning etiology and pathogenesis and, thus, the whole gives the impression of a vast amount of material, presented in a terse and almost telegraphic style. Perhaps this is best for the student who is obliged to absorb the entire content since it tends to minimize confusion and variation in interpretation.

If the book falls short of the ideal teaching text, it is not because it is incomplete, nor vague, nor disorderly. It is because, like all the others in the American field, it was obsolete before it was written. As medicine has expanded, pathology has kept pace until now it is virtually impossible for the student to learn in a single basic science course, all that is contained in the available texts. Indeed, it is wrong to expect him to. Pathology has become a course in medical orientation and as such, the emphasis has shifted from morbid anatomy to morbid physiology. For the trained pathologist, morbid anatomy has lost none of its importance, but for the student with limited time and learning capacity, the understanding of a disease entity is best achieved by the briefest possible delineation of the mechanism of the altered cell function which is at fault. Changes in cell morphology should be used simply as a visual aid in the laboratory to illustrate the lesson.

Among those who teach pathology in the classical fashion as it has been taught for the past century, Dr. Herbut's book should find a cordial welcome. Those who think that a change is needed will continue to search for a less ponderous text with a greater emphasis on morbid physiology. E. A.

BLUTKRANKHEITEN. METHODIK, KLINIK, THERAPIE. BY PROF. DR. HANNS FLEISCHHACKER. Pp. 240; 76 ills. Vienna: Wilhelm Maudrich, 1955 (Intercontinental Medical Book Corp., New York, U. S. Agents). Price, $7.50.

THIS is an excellent text on hematology written particularly for students and practitioners. The author has succeeded in presenting a subject of ever increasing complexity in simple, concise and understandable form. The subject matter is accurate and shows the author's thorough familiarity with his field, including its latest developments in all parts of the world. The illustrations are numerous and well done, with excellent color reproduction. The final chapter is a convenient summary of the blood and bone marrow changes in the more frequent infectious diseases, alphabetically arranged. The book deserves translation into English. R. K.

CLINICAL ASPECTS OF THE AUTONOMIC NERVOUS SYSTEM. BY L. A. GILLILAN, PH.D., M.D., Associate Professor of Anatomy, Graduate School of Medicine, University of Pennsylvania. Pp. 316; 42 ills. Boston: Little, Brown & Company, 1954. Price, $6.50.

THIS is, indeed, a book that should be in the library of every physician. It is not large and cumbersome but still quite complete with a most ample list of references for further reading.

The book covers a branch of medicine which is very important and relatively poorly understood and so it fills a great need. There are two parts, the first having to do with

the anatomy of the autonomic nervous system. The second covers the innervation of the visceral organs and systems with clinical applications.

All practitioners of medicine are aware of the large proportion of illnesses which results from emotional and psychological disturbances. This makes this monograph most important in the help it affords in the, at least partial, understanding of these. It is well written and easy to read as one might expect from such an able teacher, research worker and expositor. It is most heartily recommended. S. G.

CURRENT THERAPY, 1955. Edited by HOWARD F. CONN, M.D. Pp. 692. Philadelphia: W. B. Saunders Co., 1955. Price, $11.00.

THIS is the newest edition of a work which presents the latest approved methods of treatment for the practicing physician. The current volume has been prepared by 287 contributors, 85 less than the previous volume. The present volume is also shorter by 143 pages. In the main this represents an improvement, since there is less duplication. There is a commendable presentation of a number of subjects by different authors with individual therapeutic approach. There appears to be a growing restraint in the use of ACTH, cortisone and allied substances, but there is still room for more conservatism. The book should find a wide appeal. R. K.

THE CASUALTY DEPARTMENT. BY T. G. LOWDEN, M.A., B.M., B.Ch., F.R.C.S., Consultant Surgeon, Sunderland Royal Infirmary. Pp. 278; 170 ills., 12 in color. Edinburgh and London: E. & S. Livingstone, Ltd., 1955 (Williams & Wilkins Co., Baltimore, U. S. Agents). Price, $7.50.

THIS volume is an interesting one and covers the injuries and infections that one would see in this country in the average surgical outpatient department and accident dispensary. The bulk of the injuries and infections covered apply to the extremities. The last sixty pages of the book are devoted to the organization of a "casualty department" and also include a chapter on disposal of cases, legal responsibilities involved, and legal protection as applicable in the Health Service plan in force in Great Britain. The methods of treatment vary considerably in some aspects from that employed in surgical departments in the United States. This particularly applies to the treatment of acute abscesses by evacuation, internal debridement, and primary closure under penicillin sensitivity. Many of the cases that are apparently treated by the author as inpatients would be carried on an outpatient status in this country. The book is in no way a complete volume on trauma, and covers principally the most common traumatic and inflammatory lesions that are seen in the author's institution. This volume would be of moderate interest to a practicing surgeon but would in no way replace the standard American text covering similar fields. H. C.

DOCTORS IN THE SKY. THE STORY OF THE AERO MEDICAL ASSOCIATION. BY ROBERT J. BENFORD, M.D., COL. USAF (MC). Pp. 326, 53 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $8.75.

THIS is the story of aviation medicine in the United States as exemplified by the history of the Aero Medical Association. Since its founding in 1929, under its first President, Dr. Louis H. Bauer (later President of the American Medical Association in 1952) and his twenty-four distinguished successors, this society through its meetings and its journal, The Journal of Aviation Medicine, has provided the chief forum for physicians interested in the medical aspects of aviation. The author has given an excellent and highly personal portrayal of the role of medicine not only in military but in civilian aviation in this country and Canada. The book will make a warm appeal to all physicians who are air-minded. R. K.

PRINCIPLES OF ANIMAL VIROLOGY. BY F. M. BURNET, Director, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia. Pp. 486; 35 ills. New York: Academic Press, Inc., 1955. Price, $10.00.

THIS book by one of the world's most distinguished virologists is a stimulating and superbly written book. It is not a formal text in which human and animal diseases are systematically arranged. Rather it is a book concerned with certain basic biological relationships between the virus, the host and his individual cells. Included among the topics for discussion are: hemagglutination; viral multiplication and the morphological and biochemical changes that occur in the host cell; interference; immunology of viral infections; viral genetics. In his discussion of viral genetics, the author devotes considerable attention to the work on recombination in influenza viruses that has been carried on at

his institute. The quality of the discussion is at all times probing and critical and there is at all times the constant search for the important generalization. A most valuable and satisfying book. M. K.

A Synopsis of Medicine. By Sir Henry Letheby Tidy, K.B.E., M.A., M.D., Extra Physician to H. M. The Queen; Consulting Physician, St. Thomas's Hospital. 10th ed. Pp. 1253. Baltimore: Williams & Wilkins Co., 1954. Price, $7.50.

The value, popularity and durability of this standard work are attested by the appearance of this, the tenth edition, since the first in 1920, plus five reprintings. Something similar might be said about the author who has prepared the text throughout the years. The presentation of the material in outline form with liberal use of various forms of type, plus an excellent index, make the subject matter easily accessible. R. K.

Diseases of the Thyroid Gland. By Samuel L. Gargill, M.D., Assistant Clinical Professor of Medicine, and Mark F. Lesses, M.D., Instructor in Medicine, Harvard Medical School. Pp. 493; 77 ills. New York: Oxford University Press, 1955. Price, $12.00.

This text is reprinted from Oxford Loose-Leaf Medicine and contains the same page numbers as in that work.

From the vast amount of data that has accumulated in this field, the authors have taken the important contributions and have shown in a clear and concise fashion how they have led to our present concepts of thyroid physiology and pathology.

Approximately the first half of the book is devoted to a discussion of physiological and biochemical mechanisms. The role that radioactive iodine and microchemical techniques have played in the elucidation of these mechanisms is presented in an understandable way.

The second half of the book is concerned with commonly encountered types of thyroid pathology. The use of radioactive iodine in making clear many clinical phenomena and its role in the diagnosis and treatment of thyroid disease is well presented.

The text is excellently illustrated and the bibliography is quite comprehensive. Although there are more complete texts dealing with thyroid disease, this volume fills a need in that it resynthesizes the clinical and biochemical approaches to this problem.

B. C.

NEW BOOKS

Le Potassium et la vie. By Alain Reinberg, D.Sc., M.D. Pp. 128; 10 ills. Paris: Presses Universitaires de France, 1955. Price, not given.

This concisely written monograph presents and summarizes our up-to-date knowledge of potassium. It should appeal to physicists, biochemists, agriculturists and botanists, biologists, physiologists, endocrinologists, neurologists, electrocardiographers and last, but not least, to clinicians with either medical or surgical leanings.

The reviewer thinks that if any of the above mentioned "specialists" will read the chapter or chapters primarily of interest to him, he will feel compelled to read the whole booklet. The presentation is so clear and simple that possession of even a rudimentary knowledge of French should suffice. H. R.

Reflexzonenmassage in Muskulatur und Bindegewebe. By Prof. Dr. Wolfgang Kohlrausch. Pp. 134; 42 ills. Stuttgart: Hippokrates Verlag, 1955. Price, DM 22.

While reflex effects from viscera upon the skin are well known since the classical observations of H. Head and Mackenzie, the reflexes from the viscera upon the subcutaneous tissue and upon the tone of the skeletal muscles have been only occasionally studied. The author states that visceral diseases produce not only hypertonicity of the muscles but also induration of the subcutaneous tissue in the respective segments. There are also reflexes acting in the opposite direction from the surface of the body upon the viscera (cutaneo-visceral and musculo-visceral reflexes). The main body of the book deals with a detailed description of the methods attempting to reduce the segmental increases of muscle tone and the subcutaneous changes by massage and vibration. It is, of course, apparent that a favorable effect of such measures is limited by the underlying pathologic process and it is to be hoped that symptomatic subjective improvements induced by this type of massage will not unduly delay a causative treatment. E. S.

Tea. A Symposium on the Pharmacology and the Physiologic and Psychologic Effects of Tea. Edited by Henry J. Klaunberg, Ph.D., Executive Director. The Biological Sciences Foundation. Ltd. Pp. 64; 7 ills. Washington, D. C.: The Biological Sciences Foundation. Ltd., 1955. Price, $1.00.

A collection of eight papers on tea, a pleasant and useful beverage: its history, its pharmacology, its psychologic effects, its medicinal and dietary value. The most consistent con-

clusion: tea is a time-honored and popular beverage, frequently desired, seldom contraindicated.
R. S.

Expert Committee on Drugs Liable to Produce Addiction. Fifth Report. World Health Organization Technical Report Series No. 95. Pp. 16. Geneva: World Health Organization, 1955. Price, $.30.

Expert Committee on the International Pharmacopoeia. Thirteenth Report. Pp. 58. Geneva: World Health Organization, 1955.

Expert Committee on the International Pharmacopoeia. Sub-Committee on Non-Proprietary Names. Sixth Report. Pp. 11. Geneva: World Health Organization, 1955.

Ultrasonic and Ultrashort Waves in Medicine. By Johanna M. Van Went, M.D., Director, Institute for Physical Medicine and Rheumatism, Amsterdam. Pp. 384; 33 ills. Houston, Texas: Elsevier Publishing Co., 1954. Price, $9.00 .

NEW EDITIONS

Differential Diagnosis of Internal Diseases. By Julius Bauer, M.D., Clinical Professor of Medicine, College of Medical Evangelists. 2nd ed. Pp. 987; 66 ills. New York; Grune & Stratton, Inc., 1955. Price, $15.00.

This is a systematic discussion of the differential diagnosis of internal diseases. Part 1 deals with leading symptoms and conditions under which they occur. Part 2 similarly deals with leading physical signs. The presentation is clear and logical and the subject matter has been brought thoroughly up-to-date in this the second edition. There are numerous references to the pertinent literature.
R. K.

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